Bone: Aneurysmal bone cysts

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Published in Atlas Database: December 2011
Online updated version: http://AtlasGeneticsOncology.org/Tumors/AneurBoneCystID5133.html
DOI: 10.4267/2042/47329

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Clinics and pathology

Etiology
The most widely accepted pathogenetic mechanism of aneurysmal bone cysts has long involved a local circulatory disturbance leading to markedly increased venous pressure and the development of a dilated and enlarged vascular bed within the affected bone area. However, the recent identification of recurrent chromosome abnormalities has challenged this historical perception. May involve the arrest of maturation of the osteoblasts caused by USP6 overexpression and dysregulation of autocrine BMP (bone morphology protein) signaling (Lau et al., 2010).

Clinics
Aneurysmal bone cysts (ABC) are benign lesions, but locally aggressive, that occur more frequently in the metaphyses of long bones, especially distal femur, the proximal tibia and vertebral posterior bodies. Multiple involvement is frequent. It can occur at any age but most patients are diagnosed in the first 2 decades of life. It can exist as primary bone lesion or as secondary lesions arising in association with other osseous conditions, namely giant cell tumor, chondroblastoma, chondromyxoid fibroma and fibrous dysplasia. Pain and swelling are the most common complaints.

Pathology
As the name implies, the lesion is histopathologically characterized by hemorrhagic cystic and cavernous spaces surrounded by fibrous septa composed of mildly to moderately mitotically active spindle cells intermixed with scattered osteoclast-like multinucleated giant cells. Approximately 95% of ABC have typical histology whereas the remaining 5% are "solid" variants in which the usual cavernous channels and spaces may not be identified. An extraosseous counterpart of ABC has been described, sometimes referred to as ABC of soft tissues, and is histologically identical to ABC but diagnosed much less frequently.

Treatment
ABC is most frequently treated by curettage, but local recurrences can still occur in about one fourth of cases.

Cytogenetics

Cytogenetics Morphological
Chromosome bands 16q22 and/or 17p13 are non randomly rearranged in ABC, regardless of tumor type (classic, solid) and or location (osseous and extraosseous). A recurrent t(16;17)(q22;p13), with CDH11 and USP6 involvements, has been identified in at least eleven cases to date, but other chromosomal segments as translocation partner for each chromosome have been described:
- A t(1;17)(p34;p13) THRAP3/USP6 was found in one case.
- A t(3;17)(q21;p13) CNBP/USP6 was found in one case.
- A t(9;17)(q22;p13) OMD/USP6 was found in one case.
- A t(17;17)(p13;q21) COL1A1/USP6 was found in two cases.
Other translocations of note:
- one case of t(2;17)(p23;p13) (Sciot et al., 2000),
- two cases of t(6;17)(q21;p13) (Winnepenninckx et al., 2001; Althof et al., 2004),
- two cases of t(11;16)(q13;q22-23), one with a classical bone tumor, the other with a tumor of the soft tissues (Dal Cin et al., 2000; Oliveira et al., 2004),
- one case of del(16)(q22) (Panagopoulos et al., 2001),
- three cases with a t(17;17)(p13;q12) or an inv(17)(p13q11-12) (Dal Cin et al., 2000; Nielsen et al., 2002; Althof et al., 2004).
Although additional cases should be studied, it appears that in combined giant cell tumor and secondary aneurysmal bone cyst, both lesions can retain their characteristic chromosomal aberrations.

**Genes involved and proteins**

**Note**
So far, USP6 is constantly involved:
- in the t(1;17)(p34;p13) THRAP3/USP6,
- the t(3;17)(q21;p13) CNBP/USP6,
- the t(9;17)(q22;p13) OMD/USP6,
- the t(16;17)(q22;p13) CDH11/USP6,
- and the t(17;17)(p13q21) COL1A1/USP6.
However, as mentioned above, the 16q22 breakpoint has also been found recurrently in the absence of an apparent 17p13 involvement, e.g. in the t(11;16)(q13;q22-23) or in the del(16)(q22).

**USP6**
**Location**
17p13

**DNA / RNA**
7878 bp (major transcript).

**Protein**
1406 amino acids; USP6 is a hominoid-specific gene that was initially cloned from an Ewing sarcoma cell line. It arose from an evolutionary chimeric gene fusion between the TBC1D3 (also known as PRC17) and USP32 (NY-REN-60) genes, which are both located on the long arm of chromosome 17. Sequence comparisons indicate that the first 14 exons of USP6 are derived from TBC1D3 (PRC17) whereas exons 15 to 30 are derived from USP32. TBC1D3 (PRC17) is located at chromosome band 17q12 and encodes a protein with a TBC/GAP domain involved in Rab/Ypt GTPase signaling. USP32 is located at chromosome band 17q23 and encodes a protein composed of two EF-hand calcium-binding motifs, a myristoylation site, and a UBP domain. USP6 protein retains the TBC domain of TBC1D3 (PRC17) and the UBP domain of USP32. Because USP6 is absent in non-hominoid primates and is primarily expressed in testicular tissue, it has been suggested that USP6 contributed to hominoid speciation. Until recently USP6 function was poorly known but recent data suggest that USP6 is a component of a novel effector pathway for Rho GTPases Cdc42 and Rac1 and stimulates actin remodeling. USP6, also called TRE17/ubiquitin-specific protease 6 (USP6), is a deubiquitinase. It is the first de-ubiquitinating enzyme to activate NF-KB, and requires both catalytic subunits of IKK (IKKalpha and IKKbeta) (Pringle et al., 2011).

**THRAP3**
**Location**
1p34

**Protein**
THRAP3, also called TRAP150, is made of an arginine-serine-rich sequence in the N-terminal region and domains with similarity with BCLAF1 and with CASC3/MLN51 in the C-terminal region. It is part of the transcription regulatory complex TRAP/Mediator, and a component of the spliceosome. It both activates pre-mRNA splicing and induces mRNA degradation. The arginine-serine-rich N-term of THRAP3 is responsible for its splicing activity, and the C-term part for its mRNA degradation activity (Lee et al., 2010).

**CNBP**
**Location**
3q21

**Protein**
CNBP, also called ZNF9, is made of 7 CCHC-type Zn fingers. Nucleic acid binding protein; binds single stranded DNA and RNA; act as a regulator of transcription and translation of many genes, including MYC. CNBP may regulate gene expression by catalyzing the formation of G4s (G-quadruplexes, formed by intramolecular four-stranded DNA structures).

**Germinal mutations**
Myotonic dystrophy DM2 is caused by expansion of a (CCTG)(n) in CNBP. CNBP has also been implicated in sporadic inclusion body myositis (review in Calcaterra et al., 2010).

**OMD**
**Location**
9q22

**Protein**
OMD (osteomodulin), also called OSAD (osteoadherin), is a member of the small leucine rich-repeat proteoglycan (SLRP) family. It is an extracellular matrix keratan sulfate proteoglycan restricted to mineralized tissues. OMD is a marker for terminally differentiated matrix producing osteoblasts. OMD expression enhances the differentiation and maturation of osteoblasts. It is induced by osteoclast activity (Rehn et al., 2008).

**CDH11**
**Location**
16q22

**DNA / RNA**
3.6 and 3.8 kb mRNA (two major transcripts).
Protein
693 and 796 amino acids; membrane protein that mediate calcium-dependent cell-cell adhesion, member of the cadherin superfamily. CDH11 seems to be highly expressed during the development and differentiation of the osteoblastic lineage, indicating an important role in bone development. Two splice variants have been identified, one of which encodes an isoform with a shorter cytoplasmic domain. Its intracellular domain is anchored to the actin cytoskeleton through alpha and beta-catenin. Role in maintaining tissue architecture and cell polarity, limiting cell movement and beta-catenin. Role in maintaining tissue architecture anchored to the actin cytoskeleton through alpha and suppressor function.

**COL1A1**

**Location**
17q21

**Protein**
Two pro a1(I) chain associate in trimers with one pro a2(I) chain to form the type I collagen fibrils after proteolysis. Constituent of the extra cellular matrix in connective tissue of bone, skin, tendon, ligament, teeth.

**Germinal mutations**
COL1A1 has been found mutated in osteoporosis, osteogenesis imperfecta types I-IV, Ehlers-Danlos types I and VIIA, and Caffey disease (Stover and Verrelli, 2011).

### Result of the chromosomal anomaly

**Hybrid Gene**

**Description**
5' partner - 3' USP6

**Fusion Protein**

**Description**
Fusion of the promoter region of CDH11 (noncoding exons 1 and 2) to the entire coding region of USP6, which starts on exon 2 in the (16;17)(q22;p13). Therefore, there is only a fusion gene but not a fusion protein. This type of gene fusion is known as promoter swapping and has been described in other solid tumors, including pleomorphic adenoma and lipoblastoma. The same model applies to translocations of USP6 with other partners.

**Oncogenesis**
Upregulation of USP6 mediated by the highly active CDH11 (or other) promoter.

### References


This article should be referenced as such: