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# Fusion of the Lumican (*LUM*) Gene With the Ubiquitin Specific Peptidase 6 (*USP6*) Gene in an Aneurysmal Bone Cyst Carrying a t(12;17)(q21;p13) Chromosome Translocation

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**Abstract.** *Background/Aim: Aneurysmal bone cyst is a benign bone lesion with a strong tendency to recur. The rearrangement of chromosome band 17p13/USP6 gene is now considered a characteristic genetic feature of aneurysmal bone cyst, with t(16;17)(q22;p13)/CDH11-USP6 as the most frequent chromosomal aberration/fusion gene. We report a novel variant translocation leading to a new fusion gene in an aneurysmal bone cyst. Materials and Methods: Genetic analyses were performed on an aneurysmal bone cyst found in the tibia of a child. Results: G-banding chromosome analysis yielded the karyotype 46,XX,t(12;17)(q21;p13)[5]/46,XX[2]. FISH analysis with a USP6 break-apart probe showed rearrangement of USP6. RNA sequencing detected LUM-USP6 and USP6-LUM fusion transcripts which were subsequently verified by RT-PCR/Sanger sequencing. The two genes exchanged 5'- non-coding exons. Thus, promoter swapping between USP6 and LUM had taken place. Conclusion: We report a novel t(12;17)(q21;p13) chromosome translocation which gave rise to a LUM-USP6 fusion in an aneurysmal bone cyst.*

Aneurysmal bone cyst is a rapidly expanding, benign bone lesion with a strong tendency to recur (1-3). It is found in all age groups but most commonly during the first two decades of life (1-3). Aneurysmal bone cyst was originally considered a non-neoplastic lesion of unknown etiology (4). In 1999, however, Panoutsakopoulos *et al*. (5) reported three cases with clonal acquired chromosomal aberrations, two with t(16;17)(q22;p13) and one with del(16)(q22), providing evidence for a neoplastic origin of these lesions. In 2004, Oliveira *et al*. showed that the t(16;17)(q21;p13) translocation generated a fusion gene in which the strong promoter of the cadherin 11 gene (*CDH11*) at 16q21 was fused to the entire ubiquitin-specific protease 6 (*USP6*; alias Tre2) coding sequence at 17p13 (6, 7). The result of the *CDH11-USP6* chimeric gene is that *USP6* becomes transcriptionally up-regulated. Subsequently, fusion genes corresponding to the variant translocations t(1;17)(p34;p13), t(3;17)(q21;p13), t(9;17)(q22;p13), and t(17;17)(q21;p13) were reported (8). In each translocation, the entire *USP6* coding sequence was fused downstream with the promoter region of the partner gene: thyroid hormone receptor associated protein 3 (*THRAP3* at 1p34), CCHC-type zinc finger nucleic acid binding protein (*CNBP* at 3q21), osteomodulin (*OMD* at 9q22), and collagen type I alpha 1 chain (*COL1A1* at 17q21) (8). Additional studies have detected fusion of *USP6* with the genes FOS like 2, AP-1 transcription factor subunit (t(2;17)(p23;p13)/*FOSL2-USP6*), catenin beta 1 (t(3;17)(p22;p13)/*CTNNB1-USP6*), SEC31 homolog A, COPII coat complex component (t(4;17)(q21;p13)/*SEC31A-USP6*), FAT atypical cadherin 1 (t(4;17)(q35;p13)/*FAT1-USP6*), secreted protein acidic and cysteine rich (t(5;17)(q33;p13)/*SPARC-USP6*), RUNX family transcription factor 2 (t(6;17)(p21;p13)/*RUNX2-USP6*), ArfGAP with SH3 domain, ankyrin repeat and PH domain 1 (t(8;17)(q24;p13)/*ASAP1-USP6*), tenascin C (t(9;17)(q33;p13)/*TNC-USP6*), secretion associated Ras related GTPase 1A (t(10;17)(q22;p13)/*SAR1A-USP6*), eukaryotic translation initiation factor 1 (t(17;17)(p13;q21)/*EIF1-USP6*), platelet activating factor acetylhydrolase 1b regulatory subunit 1 (t(17;17)(p13;p13)/



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*Key Words:* Aneurysmal bone cyst, chromosome translocation, LUM, USP6, LUM-USP6 fusion gene.

*PAFAH1B1-USP6*), signal transducer and activator of transcription 3 (t(17;17)(p13;q21)/*STAT3-USP6*), and ubiquitin specific peptidase 9 X-linked (t(X;17)(p11;p13)/*USP9X-USP6*) in other aneurysmal bone cysts (9-13). Thus, rearrangement of chromosome band 17p13 and the *USP6* gene is now considered a characteristic genetic feature of aneurysmal bone cyst, with t(16;17)(q22;p13) as the most frequent chromosomal aberration found in 21% (9 out of 43) reported aneurysmal bone cysts with an abnormal karyotype (5, 6, 8, 12, 14-25).

Herein, we report an aneurysmal bone cyst in which a novel t(12;17)(q21;p13) translocation was found resulting in fusion of the lumican (*LUM* at 12q21) gene with *USP6*.

## Materials and Methods

*Ethics statement*. The study was approved by the Regional Ethics Committee (Regional komité for medisinsk forskningsetikk Sør-Øst, Norge, http://helseforskning.etikkom.no; 2010/1389/REK sør-øst A). Written informed consent was obtained from the patient's parents. The Ethics Committee's approval included a review of the consent procedure. All patient information has been de-identified.

*Patient*. The patient was a nine-year-old girl with post activity pain and edema in the left ankle the last couple of months. On X-ray there was an osteolytic, benign looking lesion in the metaphysis region of the distal tibia which on MRI appeared multi-locular and confined to the bone. Radiologically and on core needle biopsy aneurysmal bone cyst was the most likely diagnosis and a curettage was performed.

Histologically, the lesion was shown to be fibro-osseous (Figure 1). There was compact growth of fibrous tissue with spindled cells and focal areas with scattered osteoclast-like giant cells (Figure 1A). In some areas, there were islands of osteoid and throughout the biopsy there was osteoid production with focal calcification (Figure 1B). Some of the fibrous areas appeared to be fragments of thin walls. No atypical cells or mitotic activity were seen. The diagnosis was aneurysmal bone cyst.

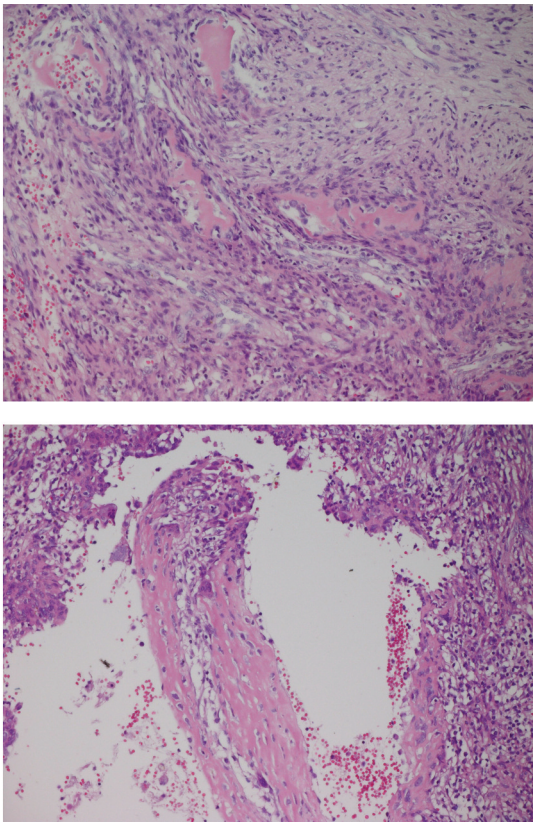


Figure 1. *Microscopic examination of the aneurysmal bone cyst. A) Hematoxylin and eosin (H&E) stained section showing compact growth of fibrous tissue with spindled cells and focal areas with scattered osteoclast-like giant cells, magnification 20×. B) H&E stained section showing cystic space and osteoid production with focal calcification, magnification 20×.*

*G-banding, karyotyping, and fluorescence in situ hybridization (FISH)*. Fresh tissue from a representative area of the tumor was analyzed cytogenetically as part of our diagnostic routine. The methodology for G-banding and karyotyping was described elsewhere (26). The samples were disaggregated mechanically and enzymatically with collagenase II (Worthington, Freehold, NJ, USA). The resulting cells were cultured and harvested using standard techniques. Chromosome preparations were G-banded with Wright's stain (Sigma-Aldrich; St Louis, MO, USA) and examined. Metaphases were analyzed and karyograms prepared using the CytoVision computer assisted karyotyping system (Leica Biosystems, Newcastle, UK). The karyotypes were reported according to the International System for Human Cytogenomic Nomenclature (27). FISH was performed on metaphase spreads using the ZytoLight SPEC *USP6* Dual Color Break Apart Probe (ZytoVision, Bremerhaven, Germany). The Probe is a mixture of an orange-labeled-probe and a green-labeled-probe which hybridize proximal and distal to the *USP6* gene, respectively. Chromosome preparations were counterstained with 0.2 μg/ml DAPI and overlaid with a 24×50 $mm^2$ coverslip. Fluorescent signals were captured and analyzed using the CytoVision system (Leica Biosystems).

*RNA sequencing*. Total RNA was extracted from frozen (–80˚C) tumor tissue adjacent to that used for cytogenetic analysis and histological examination using miRNeasy Mini Kit and Qiacube (Qiagen, Hilden, Germany). The RNA quality was evaluated using a 2100 Bioanalyzer (Agilent, Santa Clara, CA, USA) according to the manufacturer's instructions. One μg of total RNA was sent to the Genomics Core Facility at the Norwegian Radium Hospital, Oslo University Hospital (http://genomics.no/oslo/) for high-throughput paired-end RNA-sequencing. For library preparation from total RNA, the Illumina TruSeq RNA Access Library Prep kit was used according to Illumina's protocol (Illumina, San Diego, CA, USA). Sequencing was performed on NextSeq 550 System (Illumina) and 25 million reads were generated. The FASTQC software was used for quality control of the raw sequence data (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/). The software FusionCatcher was used for detection of possible fusion transcripts (28, 29).

*Confirmation of the fusion transcripts*. The presence of the fusion transcripts was confirmed by reverse transcription (RT) polymerase chain reaction (PCR) and Sanger sequencing analyses. One μg of total RNA was reverse-transcribed in a 20 μl reaction volume using

Table I. *Primers used for reverse transcription polymerase chain reaction and cycle (Sanger) sequencing. M13 forward primer (TGTAAAACGACGGCCAGT) and M13 reverse primer (CAGGAAACAGCTATGACC) sequences are in italics.*

| Name | Sequence (5'->3') | Position | Reference sequence | Gene |
|---|---|---|---|---|
| M13For-LUM-4F1 | *TGTAAAACGACGGCCAGT*-TCCGTCCTGACAGAGTTCACAGCA | 4-27 | NM_002345.4 | *LUM* |
| M13Rev-USP6-2600R1 | *CAGGAAACAGCTATGACC*-TTGAATGGTGTCCACCTGCCAAG | 2622-2600 | NM_001304284.2 | *USP6* |
| M13For-USP6-2192F1 | *TGTAAAACGACGGCCAGT*-GAGTCGGGGGAGACAATGGATGA | 2192-2214 | NM_001304284.2 | *USP6* |
| M13Rev-LUM-152-R1 | *CAGGAAACAGCTATGACC*C-TGGCCACTGGTACCACCAATCAA | 174-152 | NM_002345.4 | *LUM* |

the iScript Advanced cDNA Synthesis Kit for RT-qPCR according to the manufacturer's instructions (Bio-Rad, Hercules, CA, USA). cDNA corresponding to 20 ng total RNA was used as template in subsequent PCR assays. The BigDye Direct Cycle Sequencing Kit was used to perform both PCR and cycle (Sanger) sequencing following the company's recommendations (ThermoFisher Scientific, Waltham, MA, USA). The primer combinations were M13For-LUM-4F1/ M13Rev-USP6-2600R1 and M13For-USP6-2192F1/ M13Rev-LUM-152-R1. The primers used for RT-PCR/cycle (Sanger) are listed in Table I.

## Results

The G-banding analysis yielded a karyotype with a single chromosome abnormality: 46,XX,t(12;17)(q21;p13)[5]/ 46,XX[2] (Figure 2A). FISH analysis using the *USP6* break-apart probe showed that the distal part of the probe (green signal) hybridized to the der(12) t(12;17)(q21;p13), whereas the proximal part of the probe (red signal) hybridized to der(17) t(12;17)(q21;p13) (Figure 2B).

Using the FusionCatcher software with the fastq files from the RNA sequencing, both *LUM-USP6* and *USP6-LUM* fusion transcript sequences were detected. In the *LUM-USP6* fusion transcript, exon 1 of *LUM* (nt 97 of sequence with accession number NM_002345.4) fused to exon 9 of *USP6* (nt 2482 of sequence with accession number NM_001304284.2): CATCTGCTTTAAGAATTAACGAAAGCAGTGTCAAGAC AGTAAG/GAAACTGGGCATCTCTGTGGCCCTGAACATC CCAGGAGGCCGA. In the *USP6-LUM* fusion transcript, exon 7 of *USP6* (nt 2299 of sequence with accession number NM_001304284.2) fused to exon 2 of *LUM* (nt 98 of sequence with accession number NM_002345.4): GTGTCCTGAAC TGGGCCCTTCCTCCAGTGAGAAGCCTTCCTGA/GATTC AAACCATTTGCCAAAAATGAGTCTAAGTGCATTTACTC. RT-PCR/cycle (Sanger) sequencing verified the presence of the above-mentioned fusion transcripts (Figure 3).

## Discussion

We herein report the *LUM* gene as a new fusion partner of *USP6* in an aneurysmal bone cyst carrying a novel t(12;17)(q21;p13) chromosome translocation as the only cytogenetic aberration. The chromosome translocation resulted in fusion of the 5'-non-coding region of *USP6* with the 5'-non-coding region of *LUM* exchanging the two genes' regulatory elements. Promoter swapping between *USP6* and *LUM*, thus, took place with the expression of *USP6* coming under the control of the *LUM* promoter leading to overexpression or ectopic activation of *USP6*. The pattern in the *LUM-USP6* fusion gene was thus similar to that seen in previously reported *USP6* fusion genes (6, 8-13).

*USP6* is a hominoid-specific gene derived in the recent evolutionary past from fusion between *TBC1D3* and *USP32*, located on 17q12 and 17q23, respectively (30). The TBC (Tre-2/Bub2/Cdc16) domain of TBC1D3 and the ubiquitin binding domain of USP32 comprise the amino and carboxyl terminal parts of USP6 protein, respectively (30). Expression of *USP6* in normal tissues is predominantly found in the testis, but overexpression of *USP6* can transform mesenchymal cells, and indeed *USP6* was first identified as a potential oncogene based on its transforming properties in transfection studies of NIH-3T3 cells (31).

Overexpression or ectopic activation of *USP6* leads to deregulation of USP6-target genes and tumor formation (31-36). Recently, USP6 was found to have Frizzleds, JAK1, and JUN as substrates and consequently to promote Wnt, JAK1-STAT3, and JUN signaling pathways (35-37).

Apart from aneurysmal bone cyst, *USP6* activation by promoter-swapping gene fusion has also been found in nodular fasciitis, cranial fasciitis, and myositis ossificans (38-45). Furthermore, *USP6* rearrangements were detected in a subset of cellular fibromas of tendon sheath which share similar histological features with nodular fasciitis (46).

The *LUM* gene codes for lumican which is a member of the small leucine-rich proteoglycan family that also includes decorin, biglycan, fibromodulin, keratocan, epiphycan, and osteoglycin (47-50). Lumican is the major keratan sulfate proteoglycan of the cornea but is also distributed in interstitial collagenous matrices throughout the body (47-50). Lumican may regulate collagen fibril organization and circumferential growth, corneal transparency, and epithelial cell migration and tissue repair (48-53). In cancer, lumican was found to be involved in tumor progression, angiogenesis, and metastasis (49, 51, 52). Although most of studies showed lumican to have an anti-tumor effect, its role in cancer is

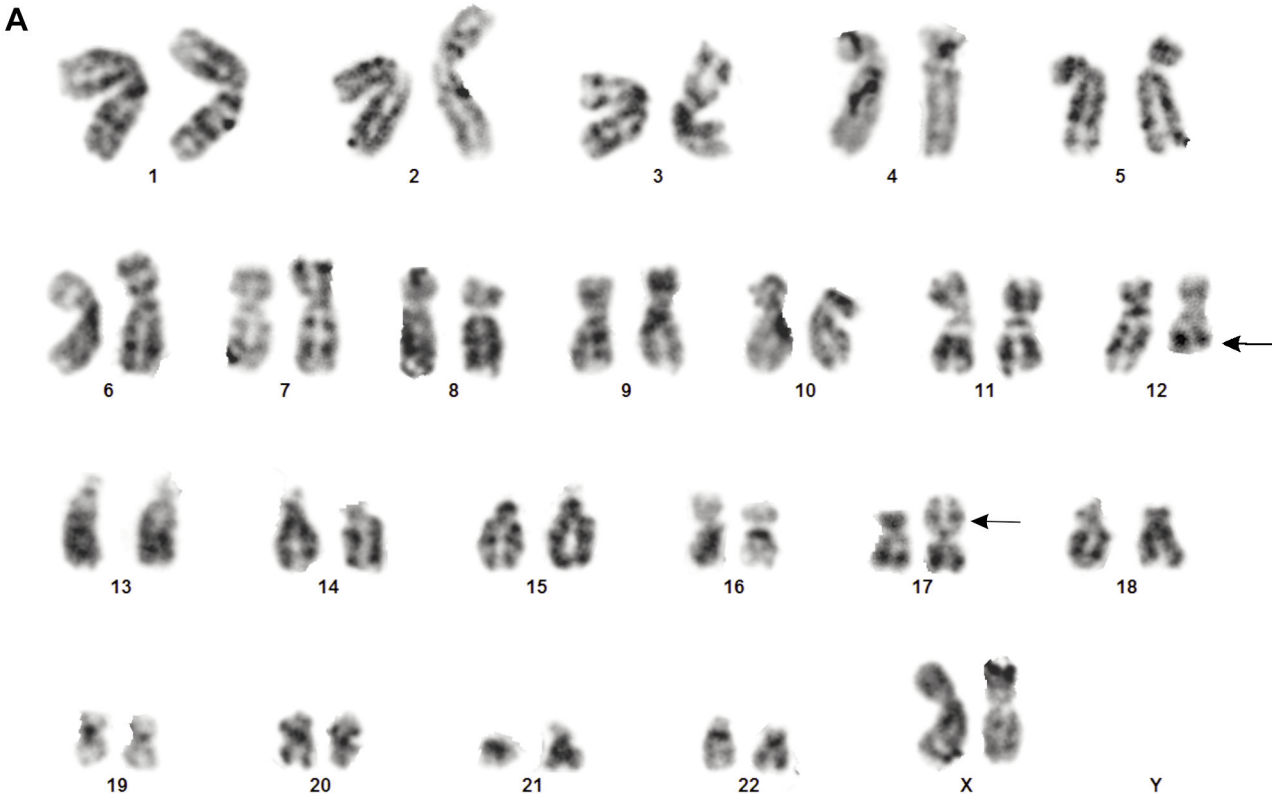


Figure 2. *G-banding and FISH analyses. A) Karyogram of the aneurysmal bone cyst cells showing the der(12)t(12;17)(q21;p13) and der(17)t(12;17)(q21;p13). Breakpoint positions are indicated by arrows. B) FISH with the USP6 break-apart probe on metaphase spread showing that the distal part of the probe (green signal) hybridized to the der(12)t(12;17)(q21;p13) whereas the proximal part of the probe (red signal) hybridized to der(17)t(12;17)(q21;p13). Both distal and proximal parts of the USP6 probe hybridized to the normal chromosome 17.*

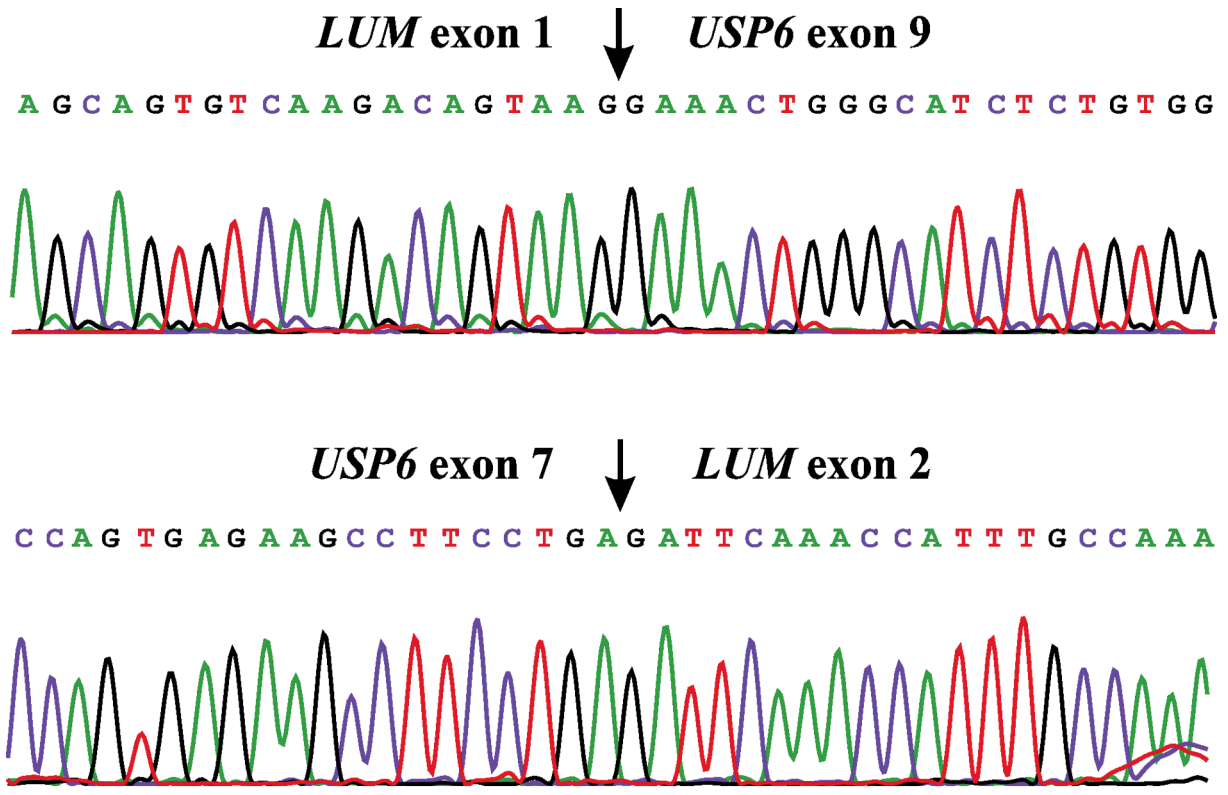


Figure 3. *Results of Sanger sequencing. Partial sequence chromatograms of the cDNA amplified fragment showing the junction position of the LUM and USP6 genes (arrow). The exon numbers were based on the sequences with accession numbers NM_002345.4 for LUM and NM_001304284.2 for USP6.*

dependent on its abundance, distribution, and tumor type and stage (49, 51, 52).

In conclusion, our finding of a novel variant t(12;17)(q21;p13) chromosome translocation with a *LUM-USP6* fusion expands the spectrum of known fusion partner genes of *USP6* and emphasizes further its central role in the pathogenesis of aneurysmal bone cyst.

## Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

## Authors' Contributions

IP designed and supervised the research, performed molecular genetic experiments and bioinformatics analysis, and wrote the article. LG performed cytogenetic analysis and evaluated the FISH data. KA performed molecular genetic experiments, FISH analyses, and evaluated the data. IL performed pathological examination. ML-I performed pathological examination. FM evaluated cytogenetic and FISH data. SH assisted with experimental design and writing of the article. All Authors read and approved the final manuscript.

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