Fusion of the \textit{COL4A5} Gene With \textit{NR2F2-AS1} in a Hemangioma Carrying a t(X;15)(q22;q26) Chromosomal Translocation

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Abstract. Background/Aim: Hemangiomas are benign neoplastic proliferations of blood vessels. Cytogenetic information on hemangiomas is limited to four tumors with abnormal karyotypes. We report here a solitary chromosomal translocation and its molecular consequence in a hemangioma.

Materials and Methods: A cavernous hemangioma was extirpated from the foot of a 62 years old man and genetically studied with cytogenetic and molecular genetic methodologies.

Results: G-Banding analysis of short-term cultured tumor cells yielded the karyotype 46,Y,t(X;15)(q22;q26)[4]/46,XY[12]. RNA sequencing detected fusion of the collagen type IV alpha 5 chain gene (COL4A5 on Xq22.3) with intronic sequences of nuclear receptor subfamily 2 group F member 2 antisense RNA 1 (NR2F2-AS1 on 15q26.2) resulting in a putative COL4A5 truncated protein. The fusion was verified by RT-PCR together with Sanger sequencing and FISH analyses.

Conclusion: The involvement of COL4A5 indicates that some hemangiomas have pathogenetic similarities with other benign tumors such as leiomyomas and subungual exostosis.

Hemangiomas are benign neoplastic proliferations of blood vessels that may develop in any vascularized tissue. Histologically, they are composed of multiple vascular channels lined with a single layer of endothelium and supported by a fibrous connective tissue scaffold (1). They occur most often in the skin or subcutaneous tissue but may also be found in skeletal muscle, bone, kidneys, lungs, colon, brain, spleen, liver, and pancreas (2-5). Hemangiomas are mostly solitary although multiple hemangioma lesions may occur in individual patients (1). The incidence and prevalence of hemangiomas are difficult to calculate since most lesions are small and asymptomatic. There are several clinical and histological subtypes (6-9).

In the present study, we report the genomic abnormalities of a cavernous hemangioma.

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-ost A). Written informed consent was obtained from the patient. The Ethics Committee’s approval included a review of the consent procedure. All patient information has been de-identified.

Case Report

The patient was a 62-year-old man with a tumor, of 3 years’ duration, on the first toe of the left foot. The tumor began as a pea-sized nodule but at the time of presenting to our Department measured 2.2×2×1.5 cm. It was not tender and moved freely against the skin and underlying structures. Magnetic resonance imaging showed a cutaneous/subcutaneous nodule of unknown etiology. Upon extirpation, the tumor was found to be well-circumscribed, consisting of blood-filled, dilated vascular structures with inconspicuous endothelial cells (Figure 1A). Between the vessels was adipose tissue (Figure 1B). The endothelial cells were immunohistochemically positive for ETS transcription factor ERG, cluster of...
Table I. Primers used for reverse transcription polymerase chain reaction and cycle (Sanger) sequencing. M13 forward primer (TGAAAACGACGGCCAGT) and M13 reverse primer (CAGGAAACGATCATGACC) sequences are in italics.

| Name                     | Sequence (5’-3’)                                                               | Position (GRCh38/hg38Assembly) |
|--------------------------|--------------------------------------------------------------------------------|---------------------------------|
| M13For-COL4A5-F1         | TGGAAAACGACGGCCAGT-CCTCCTGGATTACCTGTTCCATCA                                      | chrX:10861762-10861785          |
| M13Rev-NR2F2A5-S1R1      | CAGGAAACGATCATGACC-CCCAAATTTTTCTAGCGCAAATG                                      | chr15:96227351-96227373         |
| M13Rev-NR2F2A5-S2R1      | CAGGAAACGATCATGACC-TGGCGTAGAGGCTCCAAGAGATCA                                      | chr15:96172670-96172692         |
| M13Rev-NR2F2A5-S3R1      | CAGGAAACGATCATGACC-CCTCATGCTTCCAGTGCTG                                          | chr15:96173857-96173880         |

RT-qPCR and cycle (Sanger) sequencing. One μg of total RNA was reverse-transcribed in a 20 μL reaction volume using 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 according to the company’s recommendations (ThermoFisher Scientific, Waltham, MA, USA). The primer combinations for collagen type IV alpha 5 (COL4A5) were M13For-COL4A5-F1/M13Rev-NR2F2A5-S1R1, M13For-COL4A5-F1/M13Rev-NR2F2A5-S2R1, and M13For-COL4A5-F1/M13Rev-NR2F2A5-S3R1. The primers used for RT-PCR/cycle (Sanger) sequencing are listed in Table I.

Results

G-Banding analysis yielded a karyotype with a single chromosomal translocation: 46,XY,t(X;15)[4] (Figure 2).

Using the deFuse software on the fastq files of the RNA sequencing data, three fusion transcripts of the COL4A5 gene were identified with intronic sequences from the locus NR2F2-AS1 on 15q26.2. Two signals were found (Seq1, Seq2, and Seq3 in Figure 3), resulting in a putative COL4A5 truncated protein. RT-PCR/cycle (Sanger) sequencing verified the presence of the above-listed fusion transcripts (Figure 3).

Interphase FISH analyses showed the normal male pattern of one red (COL4A5 probe, Xq22) and two green signals (NR2F2-AS1 probe, 15q26) in 72 nuclei, whereas the abnormal fusion pattern of two yellow signals and one green signal was seen in 28 nuclei (Figure 4).

differentiation 31 (CD31), and cluster of differentiation 33 (CD34) but negative for podoplanin (antibody D2-40). The diagnosis was cavernous hemangioma (Figure 1).

G-Banding and karyotyping. Fresh tissue from a representative area of the tumor was cultured short-term and analyzed cytogenetically as previously described (10). The karyotype was written according to the International System for Human Cytogenomic Nomenclature (11).

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 (Qiagen, Hilden, Germany). One microgram 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. The software deFuse was used for detection of possible fusion transcripts (12).

Confirmation of fusion transcripts. The actual presence of the fusion transcripts (see below) was confirmed by reverse transcription polymerase chain reaction (RT) polymerase chain reaction (PCR) and Sanger sequencing. One μg of total RNA was reverse-transcribed in a 20 μL reaction volume using 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 according to the company’s recommendations (ThermoFisher Scientific, Waltham, MA, USA). The primer combinations for collagen type IV alpha 5 chain gene (COL4A5) were M13For-COL4A5-F1/M13Rev-NR2F2A5-S1R1, M13For-COL4A5-F1/M13Rev-NR2F2A5-S2R1, and M13For-COL4A5-F1/M13Rev-NR2F2A5-S3R1. The primers used for RT-PCR/cycle (Sanger) sequencing are listed in Table I.

Fluorescence in situ hybridization (FISH). BAC clones were retrieved from the RPCI-11 Human BAC library (Human 32K clone set, BACPAC Resources Center, https://bancpacresources.org/pHumanMinSet.htm). They were selected according to physical and genetic mapping data on chromosomes X and 15 (see below) as reported on the Human Genome Browser at the University of California, Santa Cruz website [https://genome.ucsc.edu/; 2013 (GRCh38/hg38) assembly]. For COL4A5 on Xq22.3, the BAC clone used was RP11-815E21 (position: chrX:108600939-108762248). For the NR2F2-AS1 gene on 15q26.2, the probe used consisted of the BAC clones RP11-4G2 (accession number: AC018574.6, position: chr15:95,875,102-96,046,959) and RP11-522B15 (accession number: AC087477.8, position: chr15:96,350,179-96,541,611). The COL4A5 probe was labelled with Texas Red-5-dCTP (PerkinElmer, Boston, MA, USA) in order to obtain a red signal. The probe for NR2F2-AS1 was labelled with fluorescein-12-dCTP (PerkinElmer) in order to obtain green signals. FISH mapping of the probes on normal controls was performed to confirm their chromosomal location. Chromosomal preparations were counterstained with 0.2 μg/ml 4’,6-diamidino-2-phenylindole, and overlaid with a 24×50 mm2 coverslip. Fluorescent signals were captured and analyzed using the CytoVision system (Leica Biosystems, Newcastle upon Tyne, UK). Detailed information on the FISH procedure is provided elsewhere (13).
Discussion

We present here a hemangioma carrying a t(X;15)(q22;q26) as the sole chromosome abnormality. This translocation, which to our knowledge has never been described in neoplasia (14), recombined COL4A5 from Xq22 with NR2F2-AS1 from 15q26 generating a COL4A5–NR2F2-AS1 fusion gene. Rearrangements of the COL4A5 gene were, however, found in five subungual exostoses carrying the translocation t(X;6)(q13-14; q22) (15). In four of those cases, the breakpoint mapped to the 3′-region of COL4A5, whereas in the fifth tumor, it was slightly telomeric of COL4A5 (15).

The COL4A5 gene is transcribed from centromere to telomere and encodes one of the six subunits of type IV collagen, the major structural component of basement membranes (16, 17). COL4A5 is paired head-to-head with COL4A6, sharing a bidirectional promoter (18, 19). Mutations in this gene are associated with the X-linked Alport syndrome, also known as hereditary nephritis (16, 17, 20, 21). Deletions of the 5′-ends of both COL4A5 and COL4A6, including the intergenic region, were found in Alport syndrome associated with diffuse leiomyomatosis (22-26). Furthermore, whole-genome sequencing analysis showed that a subset of uterine leiomyomas harbored somatic deletions within the COL4A5–COL4A6 locus (27). Somatic deletion of the 5′-ends of both COL4A5 and COL4A6 was also found in an esophageal leiomyoma (28).

NR2F2-AS1 was found to promote cell proliferation in prostate carcinoma and lung cancer (29, 30). Down-regulation of NR2F2-AS1 induced G1 arrest of colorectal cancer cells and inhibited proliferation/induced apoptosis of nasopharyngeal carcinoma cells (29, 30). Next and telomeric to NR2F2-AS1 is the NR2F2 gene, which is transcribed from centromere to telomere and in which alternate splicing results in multiple transcript variants (https://www.ncbi.nlm.nih.gov/gene/7026). NR2F2 codes for a member of the steroid thyroid hormone superfamily of nuclear receptors, a ligand-inducible transcription factor involved in the regulation of many different genes (31, 32). A possible consequence of the t(X;15)(q22;q26) might also be deregulation of NR2F2 in a manner similar to that which occurs with the fusion of the collagen type I alpha 1 chain gene (COL1A1) with the platelet-derived growth factor subunit B gene (PDFGB), the ubiquitin specific peptidase 6 gene (USP6), and FYN proto-oncogene, Src family tyrosine kinase gene (FYN) in dermatofibrosarcoma protuberos, aneurysmal bone cyst, and epithelioid osteoblastoma, respectively (33-37). Thus, the expression of NR2F2 is under control of the COL4A5 promoter.

There are several different clinical and histological subtypes of hemangioma (6-8, 38, 39), some of which were also known to have genetic aberrations. Rearrangements of the Fos proto-oncogene, AP-1 transcription factor subunit (FOS) gene (14q24) were found to be frequent in epithelioid hemangiomas (40, 41), whereas a fusion of ZFP36 ring finger
Figure 3. Results of the RNA and Sanger sequencing. A: The three collagen type IV alpha 5 chain–nuclear receptor subfamily 2 group F member 2 antisense RNA 1 (COL4A5–NR2F2-AS1) fusion sequences obtained from the RNA sequencing data after analysis using the deFuse software package. The primers used are in color. B: Partial sequence chromatograms of the cDNA amplified fragment showing the junction position of COL4A5 and the three sequences from NR2F2-AS1 (arrow).
Figure 4. Fluorescence in situ hybridization (FISH) analysis of the hemangioma using a home-made, dual color fusion probe for the detection of the chimeric gene collagen type IV alpha 5 chain–NR2F2 antisense RNA 1 (COL4A5–NR2F2-AS1). A: Ideogram of the X chromosome showing the mapping position of the COL4A5 gene at Xq22.3 (vertical red line). B: Diagram showing the FISH probe RP11-815E21 for COL4A5. The neighboring insulin receptor substrate 4 gene (IRS4) is also shown. The exons of COL4A5 found in fusion sequences using the deFuse software are shown (RNA sequencing). C: Ideogram of chromosome 15 showing the mapping position of the NR2F2-AS1 gene at 15q26.2 (green box). D: Diagram showing the FISH probes RP11-4G2 and RP11-522B15 for NR2F2-AS1. The neighboring NR2F2 gene in this region is also shown. Seq1, Seq2, and Seq3 (vertical lines) show the positions of the sequences which were found in the COL4A5–NR2F2-AS1 fusion. E: FISH results with the COL4A5 (red signal) and NR2F2-AS1 (green signal) probes on interphase nuclei. A nucleus with normal male pattern (one red and two green signals) and a nucleus with COL4A5–NR2F2-AS1 fusion (one green and two yellow/fusion signals) are shown.
protein gene (ZFP36) with FosB proto-oncogene, AP-1 transcription factor subunit gene (FOSB) was shown to define a subset of epithelioid hemangioma with atypical features (42). ZFP36 and FOSB map to 19q13.2 and 19q13.32, respectively. Somatic mutations in the G protein subunit alpha q (GNAQ on 9q21.2) and G protein subunit alpha 11 (GNA11 on 19p13.3) genes were found in congenital hemangioma (43) whereas somatic mutations of isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2) genes were found in spindle-cell hemangiomas (44-46). A fusion of the EWS RNA binding protein 1 gene (EWSR1) with the nuclear factor of activated T-cells 1 gene (NFATC1) was found in a hemangioma of the bone carrying a t(18;22)(q23;q12) translocation as the sole karyotypic change (47), and a fusion of the TBL1X receptor 1 gene (TBLIXR1) with the high mobility group AT-hook 1 gene (HMGA1) was detected in a splenic hemangioma with the translocation t(3;6)(q26;p21) (10). Two other hemangiomas of the nasal cavity/paranasal sinuses also had chromosomal aberrations. The first of those two was a cavernous hemangioma that underwent transformation to an angiosarcoma; it showed trisomy 5 together with loss of the Y chromosome upon karyotyping (48). The second, a lobular capillary hemangioma of the nasal cavity, carried a del(21)(q21q22) as the only cytogenetic aberration (49).

The data already published together with what we describe here therefore indicate that hemangiomas generally are characterized by simple chromosomal aberrations which sometimes generate fusion genes. The available information does not yet allow more specific conclusions as to how these tumors develop, however. Nevertheless, the involvement of HMGA1 and COL4A5 does indicate that, at least in some hemangiomas, the pathogenetic mechanisms are similar to those of other benign connective tissue tumors such as leiomyomas and subungual exostoses.

Conflicts of Interest

The Authors declare that they have no potential 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. IL performed pathological examination. KA performed molecular genetic experiments, FISH analyses, and evaluated the data. ML-I performed pathological examination. FM supervised the research. SH assisted with experimental design and writing of the article. All authors read and approved of the final article.

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References

1 Elsayes KM, Menias CO, Dillman JR, Platt JF, Willatt JM and Heiken JP: Virtual malformation and hemangiomatosis syndromes: Spectrum of imaging manifestations. Am J Roentgenol 190(5): 1291-1299, 2008. PMID: 18430846. DOI: 10.2214/AJR.07.2779
2 Calandrelli L, Grimaldi G, Petrone G, Rigante M, Petroni S, Riso M and Savino G: Cavernous venous malformation (cavernous hemangioma) of the orbit: Current concepts and a review of the literature. Surv Ophthalmol 62(4): 393-403, 2017. PMID: 28131871. DOI: 10.1016/j.survophthal.2017.01.004
3 Mondal U, Henkes N, Henkes D and Rosenkranz L: Cavernous hemangioma of adult pancreas: A case report and literature review. World J Gastroenterol 21(33): 9793-9802, 2015. PMID: 26361427. DOI: 10.3748/wjg.v21.i33.9793
4 Vilanova JC, Barcelo J, Smirniotopoulos JG, Perez-Andres R, Villalon M, Miro J, Martin F, Capellades J and Ros PR: Hemangioma from head to toe: MR imaging with pathologic correlation. Radiographics 24(2): 367-385, 2004. PMID: 15026587. DOI: 10.1148/rg.242035079
5 Wierzbicki JM, Henderson JH, Scarborough MT, Bush CH, Reith JD and Clugston JR: Intramuscular hemangiomas. Sports Health 5(5): 448-454, 2013. PMID: 24427416. DOI: 10.1177/1941738112470910
6 LeBoit PE, Burg G, Weedon D and Sarasin A: WHO Classification of Tumours. Pathology and Genetics of Skin Tumours. IARC: Lyon, 2006.
7 Kansdorf MJ, Murphey MD and Faxedur-Smith JC: Classification of benign vascular lesions: History, current nomenclature, and suggestions for imagers. Am J Roentgenol 197(1): 8-11, 2011. PMID: 21701004. DOI: 10.2214/AJR.10.5962
8 Fletcher CDM, Bridge JA, Hogendoorn PCW and Mertens F: WHO Classification of Tumours of Soft Tissue and Bone. International Agency for Research on Cancer (IARC): Lyon, France, 2013.
9 Colonje JE: Haemangiomas. In: WHO Classification of Tumours of Soft Tissue and Bone. Fourth Edition. Fletcher CDM, Bridge JA, Hogendoorn PCW and Mertens F (eds.). International Agency for Research on Cancer (IARC): Lyon, France, pp 138-140, 2015.
10 Panagopoulos I, Gorunova L, Bjerkehagen B, Lobmaier I and Heim S: Fusion of the TBLIXR1 and HMGA1 genes in splenic hemangioma with t(3;6)(q26;p21). Int J Oncol 48(3): 1242-1250, 2016. PMID: 26708416. DOI: 10.3829/ijo.2015.3310
11 McGowan-Jordan J, Simons A and Schmid M: ISCN 2016: An International System for Human Cytogenomic Nomenclature. Karger: Basel, pp 140, 2016.
12 McPherson A, Hormozdari F, Zayed A, Giuliani R, Ha G, Sun MG, Griffith M, Heravi Moussavi A, Senz J, Melnyk P, Nachev M, Marra MA, Hirst M, Nielsen TO, Sahinalp SC, Huntsman D and Shah SP: deFuse: An algorithm for gene fusion discovery in tumor RNA-Seq data. PLoS Comput Biol 7(5): e1001138, 2011. PMID: 21625565. DOI: 10.1371/journal.pcbi.1001138
13 Panagopoulos I, Bjerkehagen B, Gorunova L, Taksdal I and Heim S: Rearrangement of chromosome bands 12q14-15 causing HMGA2-SOX5 gene fusion and HMGA2 expression in extraskeletal osteochondroma. Oncol Rep 34(2): 577-584, 2015. PMID: 26043835. DOI: 10.3892/or.2015.4035
14 Miettinen Database of Chromosome Aberrations and Gene Fusions in Cancer. 2020 Available at: http://mitelmandatabase.isb-cgc.org/ [Last accessed on 5th March 2020]
15 Storlazzi CT, Wozniak A, Panagopoulos I, Sciort R, Mandahl N, Mertens F and Debiec-Rychter M: Rearrangement of the COL2A1 and COL4A5 genes in subungual exostosis: Molecular cytogenetic delineation of the tumor-specific translocation t(X;6)(q13-14;q22). Int J Cancer 118(8): 1972-1976, 2006. PMID: 16284948. DOI: 10.1002/jic.21586

16 Cosgrove D and Liu S: Collagen IV diseases: A focus on the glomerular basement membrane in Alport syndrome. Matrix Biol 57-58(1): 45-54, 2017. PMID: 27576055. DOI: 10.1016/j.matbio.2016.08.005

17 Pozzi A, Yurchenco PD and Iozzo RV: The nature and biology of basement membranes. Matrix Biol 57-58(1): 1-11, 2017. PMID: 28040522. DOI: 10.1016/j.matbio.2016.12.009

18 Sado Y, Kagawa M, Naito I, Ueki Y, Seki T, Momota R, Oohashi T and Ninomiya Y: Organization and expression of basement membrane collagen IV genes and their roles in human disorders. J Biochem 123(5): 767-776, 1998. PMID: 9562604. DOI: 10.1093/oxfordjournals.jbchem.a022003

19 Sund M, Maeshima Y and Kalluri R: Bifunctional promoter of type IV collagen COL4A5 and COL4A6 genes regulates the expression of alpha5 and alpha6 chains in a distinct cell-specific fashion. Biochem J 387(Pt 3): 755-761, 2005. PMID: 15598179. DOI: 10.1042/BJ20041870

20 Savige J, Storey H, Il Cheong H, Gung Kang H, Park E, Hilbert P, Persikov A, Torres-Fernandez C, Ars E, Torra R, Hertz JM, Thomassen M, Shagam L, Wang D, Wang Y, Flinter F and Nagel M: X-Linked and autosomal recessive Alport syndrome: Pathogenic variant features and further genotype-phenotype correlations. PLoS One 11(9): e0161802, 2016. PMID: 27627812. DOI: 10.1371/journal.pone.0161802

21 Nozu K, Nakanishi K, Abe Y, Udagawa T, Okada S, Okamoto S, Savige J, Storey H, Il Cheong H, Gyung Kang H, Park E, Hilbert P, Persikov A, Torres-Fernandez C, Ars E, Torra R, Hertz JM, Thomassen M, Shagam L, Wang D, Wang Y, Flinter F and Nagel M: X-Linked and autosomal recessive Alport syndrome: Pathogenic variant features and further genotype-phenotype correlations. PLoS One 11(9): e0161802, 2016. PMID: 27627812. DOI: 10.1371/journal.pone.0161802

22 Heidet L, Boye E, Cai Y, Sado Y, Zhang X, Flejou JF, Fekete F, Ninomiya Y, Gubler MC and Antignac C: Somatic deletion of the 5’ ends of both the COL4A5 and COL4A6 genes in a sporadic lesion of the esophagus. Am J Pathol 152(3): 673-678, 1998. PMID: 9502408.

23 Fu X, Wang D, Shu T, Cui D and Fu Q: LncRNA NR2F2-AS1 positively regulates CDK4 to promote cancer cell proliferation in prostate carcinoma. Aging Male: 1-7, 2019. PMID: 31566058. DOI: 10.1080/13685538.2019.1670157

24 Zhang S, Zhang X, Sun Q, Zhuang C, Li G, Sun L and Wang H: LncRNA NR2F2-AS1 promotes tumourigenesis through modulating BMI1 expression by targeting mir-320b in non-small cell lung cancer. J Cell Mol Med 23(3): 2001-2011, 2019. PMID: 30592135. DOI: 10.1111/jcc.14102

25 Ashraf UM, Sanchez ER and Kumarasamy S: COUP-TFI revisited: Its role in metabolic gene regulation. Steroids 141: 63-69, 2019. PMID: 30481528. DOI: 10.1016/j.steroids.2018.11.013

26 Polvani S, Pepe S, Milan S and Galli A: COUP-TFI in health and disease. Cells 9(1): 101, 2020. PMID: 31906104. DOI: 10.3390/cells9010101

27 Oliveira AM, Perez-Atayde AR, Dal Cin P, Gebhardt MC, Chen CJ, Neff JR, Demetri GD, Rosenberg AE, Bridge JA and Fletcher JA: Anomalous bone cyst variant translocations upregulate USP6 transcription by promoter swapping with the ZNF9, COL1A1, TRAP150, and OMD genes. Oncogene 24(21): 3419-3426, 2005. PMID: 15735689. DOI: 10.1038/sj.onc.1208506

28 Panagopoulos I, Mertens F, LoFenven R and Mandahl N: Fusion of the COL1A1 and USP6 genes in a benign bone tumor. Cancer Genet Cytoangen 180(1): 70-73, 2008. PMID: 18068538. DOI: 10.1016/j.cancergenetcyto.2007.09.017

29 Llombart B, Sanmartin O, Lopez-Guerrero JA, Monteagudo C, Giacchero D, Maire G, Nuin PA, Berthier F, Ebran N, Carlotti CJ, Neff JR, Demetri GD, Rosenberg AE, Bridge JA and Fletcher JA: Anomalous bone cyst variant translocations upregulate USP6 transcription by promoter swapping with the ZNF9, COL1A1, TRAP150, and OMD genes. Oncogene 24(21): 3419-3426, 2005. PMID: 15735689. DOI: 10.1038/sj.onc.1208506

30 Panagopoulos I, Mertens F, Lofwenberg R and Mandahl N: Fusion of the COL1A1 and USP6 genes in a benign bone tumor. Cancer Genet Cytoangen 180(1): 70-73, 2008. PMID: 18068538. DOI: 10.1016/j.cancergenetcyto.2007.09.017

31 Ashraf UM, Sanchez ER and Kumarasamy S: COUP-TFI revisited: Its role in metabolic gene regulation. Steroids 141: 63-69, 2019. PMID: 30481528. DOI: 10.1016/j.steroids.2018.11.013

32 Polvani S, Pepe S, Milan S and Galli A: COUP-TFI in health and disease. Cells 9(1): 101, 2020. PMID: 31906104. DOI: 10.3390/cells9010101

33 Oliveira AM, Perez-Atayde AR, Dal Cin P, Gebhardt MC, Chen CJ, Neff JR, Demetri GD, Rosenberg AE, Bridge JA and Fletcher JA: Anomalous bone cyst variant translocations upregulate USP6 transcription by promoter swapping with the ZNF9, COL1A1, TRAP150, and OMD genes. Oncogene 24(21): 3419-3426, 2005. PMID: 15735689. DOI: 10.1038/sj.onc.1208506

34 Panagopoulos I, Mertens F, LoFenven R and Mandahl N: Fusion of the COL1A1 and USP6 genes in a benign bone tumor. Cancer Genet Cytoangen 180(1): 70-73, 2008. PMID: 18068538. DOI: 10.1016/j.cancergenetcyto.2007.09.017

35 Llombart B, Sammartin O, Lopez-Guerrero JA, Monteagudo C, Serra C, Requena C, Poveda A, Vistos JL, Almenar S, Llombart-Bosch A and Guillon C: Dermatofibrosarcoma protuberans: Clinical, pathological, and genetic (COL1A1-PDGFB) study with therapeutic implications. Histopathology 54(7): 860-872, 2009. PMID: 19635106. DOI: 10.1111/j.1365-2559.2009.03310.x

36 Giacchero D, Maire G, Nuin PA, Berthier F, Ebran N, Carlotti CJ, Neff JR, Demetri GD, Rosenberg AE, Bridge JA and Fletcher JA: Anomalous bone cyst variant translocations upregulate USP6 transcription by promoter swapping with the ZNF9, COL1A1, TRAP150, and OMD genes. Oncogene 24(21): 3419-3426, 2005. PMID: 15735689. DOI: 10.1038/sj.onc.1208506

37 Panagopoulos I, Gorunova L, Lobmaier I, Lund-Iversen M, Andersen K, Holth A, Bjerkehagen B and Heim S: Fusion of the COL1A1 and USP6 genes in a benign bone tumor. Cancer Genet Cytoangen 180(1): 70-73, 2008. PMID: 18068538. DOI: 10.1016/j.cancergenetcyto.2007.09.017
38 Hameed M and Wold LE: Haemangioma. In: WHO Classification of Tumours of Soft Tissue and Bone. Fourth Edition. Fletcher CDM, Bridge JA, Hogendoorn PCW and Mertens F (eds.). International Agency for Research on Cancer (IARC): Lyon, France, pp. 332, 2013.

39 Rosenberg AE and Bovée JVMG: Epithelioid haemangioma. In: WHO Classification of Tumours of Soft Tissue and Bone. Fourth Edition. Fletcher CDM, Bridge JA, Hogendoorn PCW and Mertens F (eds.). International Agency for Research on Cancer (IARC): Lyon, France, pp. 333-334, 2013.

40 Huang SC, Zhang L, Sung YS, Chen CL, Krausz T, Dickson BC, Kao YC, Agaram NP, Fletcher CDM and Antonescu CR: Frequent FOS gene rearrangements in epithelioid hemangioma: A molecular study of 58 cases with morphologic reappraisal. Am J Surg Pathol 39(10): 1313-1321, 2015. PMID: 26135557 . DOI : 10.1097/ Pas.0000000000000469

41 van IJzendoorn DG, de Jong D, Romagosa C, Picci P, Benassi MS, Gamarotti M, Daugaard S, van de Sande M, Szuhai K, French PJ and Bovee JVMG: Fusion events lead to truncation of FOS in epithelioid hemangioma of bone. Genes Chromosomes Cancer 54(9): 565-574, 2015. PMID: 26173738 . DOI : 10.1002/ gcc.22269

42 Antonescu CR, Chen HW, Zhang L, Sung YS, Panicek D, Agaram NP, Dickson BC, Krausz T and Fletcher CD: ZF P36-FOSB fusion defines a subset of epithelioid hemangioma with atypical features. Genes Chromosomes Cancer 53(11): 951-959, 2014. PMID: 25043949 . DOI : 10.1002/ gcc.22206

43 Ayturk UM, Couto JA, Hann S, Mulliken JB, Williams KL, Huang AY, Fishman SJ, Boyd TK, Kozakewich HPW, Bischoff J, Greene AK and Warman ML: Somatic activating mutations in GNAQ and GNAI1 are associated with congenital hemangioma. Am J Hum Genet 98(4): 789-795, 2016. PMID: 27058448 . DOI : 10.1016/j.ajhg.2016.03.009

44 Kurek KC, Pansuriya TC, van Ruler MAJH, van den Akker B, Luks VL, Verbeke SLJ, Kozakewich HP, Sciot R, Lev D, Lazar AJ, Fletcher CDM and Bovée JVMG: R132C IDH1 mutations are found in spindle-cell hemangiomas and not in other vascular tumors or malformations. Am J Pathol 182(5): 1494-1500, 2013. PMID: 23485734 . DOI : 10.1016/j.ajpath.2013.01.012

45 Pansuriya TC, van Eijk R, d’Adamo P, van Ruler MAJH, Kuijjer ML, Oosting J, Clayton-Jansen AM, van Oosterwijk JG, Verbeke SLJ, Meijer D, van Wezel T, Nord KH, Sangiorgi L, Toker B, Liegl-Atzwanger B, San-Julian M, Sciot R, Limaye N, Kindblom LG, Daugaard S, Godfraind C, Boon LM, Vikkula M, Kurek KC, Szuhai K, French PJ and Bovee JVMG: Somatic mosaic IDH1 and IDH2 mutations are associated with enchondroma and spindle cell hemangioma in Ollier disease and Maffucci syndrome. Nat Genet 43(12): 1256-1261, 2011. PMID: 22055352 . DOI : 10.1038/ng.1004

46 Ten Broek RW, Bekers EM, de Leng WWJ, Strengeaman E, Tops BBJ, Kutzner H, Leeuwis JW, van Gorp JM, Creytens DH, Mentzel T, van Diest PJ, Eijkelenboom A and Flucce U: Mutational analysis using sanger and next generation sequencing in sporadic spindle cell hemangiomas: A study of 19 cases. Genes Chromosomes Cancer 56(12): 855-860, 2017. PMID: 28845532 . DOI : 10.1002/ gcc.22501

47 Arbajian E, Magnusson L, Brosjo O, Wejde J, Folpe AL, Nord KH and Mertens F: A benign vascular tumor with a new fusion gene: EWSRI-NFATC1 in hemangioma of the bone. Am J Surg Pathol 37(4): 613-616, 2013. PMID: 23480895 . DOI : 10.1097/PAS.0b013e31827ae13b

48 Mandahl N, Jin YS, Heim S, Willen H, Wennerberg J, Biorklund A and Mitelman F: Trisomy 5 and loss of the Y chromosome as the sole cytogenetic anomalies in a cavernous hemangioma/angiosarcoma. Genes Chromosomes Cancer 1(4): 315-316, 1990. PMID: 2278963 . DOI : 10.1002/gcc.2870010410

49 Truss L, Dobin SM and Donner LR: Deletion (21)(q21.2q22.12) as a sole clonal cytogenetic abnormality in a lobular capillary hemangioma of the nasal cavity. Cancer Genet Cytogetnet 170(1): 69-70, 2006. PMID: 16965959 . DOI : 10.1016/j.cancergencyto.2006.04.016

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