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Chromosomal Translocation t(5;12)(p13;q14) Leading to Fusion of High-mobility Group AT-hook 2 Gene With Intergenic Sequences From Chromosome Sub-Band 5p13.2 in Benign Myoid Neoplasms of the Breast: A Second Case

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Abstract. *Background/Aim: Recently, we reported a myoid hamartoma carrying a t(5;12)(p13;q14) karyotypic aberration leading to fusion of the high-mobility group AT-hook 2 (HMGA2) gene with a sequence from chromosome sub-band 5p13.2. We describe here another benign myoid tumor of the breast with identical genetic aberrations. Materials and Methods: A mammary leiomyomatous tumor found in a 45-year-old woman was studied using cytogenetics, fluorescence in situ hybridization, RNA sequencing, reverse transcription-polymerase chain reaction and Sanger sequencing. Results: The karyotype of the tumor cells was 46,XX,t(5;12)(p13;q14)[14]. Fluorescence in situ hybridization showed rearrangement of HMGA2, RNA sequencing detected fusion of HMGA2 with a sequence from 5p13.2, whereupon reverse transcription-polymerase chain reaction together with Sanger sequencing verified the HMGA2-fusion transcript. The results were identical to those obtained by us previously in a myoid hamartoma of the breast. Conclusion: The translocation t(5;12)(p13;q14) and fusion of HMGA2 with sequences from sub-band 5p13.2 appear to be recurrent events in benign mammary myoid neoplasms.*

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Key Words: Myoid hamartoma of the breast, leiomyoma, myoid neoplasm, chromosomal translocation t(5;12)(p13;q14), *HMGA2* rearrangement, intergenic sequence, chromosome sub-band 5p13.2.

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Hamartomas (from Greek hamartia, meaning error, mistake, fault, failure, defect) are benign malformation-type tumors that may be found in almost any part of the body (1, 2). They were first described by the German pathologist Eugen Albrecht in 1904 who defined them as "tumor-like formations in which we can demonstrate abnormal mixture of normal components of the organ in which they occur either by amount, structure, degree of maturity, or all three together" (3). He also assumed that "the formation of these above growths took place by abnormal mixing or fundamental disturbance in the course of development" (3).

In 1971, Arrigoni and co-workers used the term mammary hamartoma to describe a well-circumscribed breast lesion with varying amounts of benign epithelial elements, fibrous tissue, and fat (4). Two years later, Davies and Riddell described myoid (muscular) hamartoma of the breast as a subtype of breast hamartomas characterized by the additional presence of smooth muscle cells (5).

Judging by the publication record, myoid hamartomas of the breast are very rare benign lesions, most of which have been reported as single cases (6-25). The differential diagnosis of myoid hamartoma includes various tumor-like lesions showing smooth muscle differentiation and spindle-cell tumors including fibroadenoma, myofibroblastoma, leiomyoma, and leiomyosarcoma (6-25).

Differential diagnosis of the many phenotypically somewhat variable benign myoid lesions that can be found in the breast is not always possible nor is it necessarily clinically relevant (21, 22, 25). Nevertheless, a general histological description of myoid hamartoma of the breast is

that the prominent smooth muscle component is mixed with other breast elements such as adipose tissue, fibrous stroma, and glandular tissue (22, 25).

Recently, our group reported the first genetically analyzed myoid hamartoma of the breast (23). The lesion had a t(5;12)(p13;q14) translocation as the sole karyotypic aberration. Using fluorescence *in situ* hybridization (FISH), RNA sequencing, reverse transcription-polymerase chain reaction (RT-PCR), and Sanger sequencing methodologies, we demonstrated that the molecular consequence of the translocation was fusion of the high-mobility group AT-hook 2 (*HMGA2*) gene from 12q14 with a sequence from chromosome sub-band 5p13.2. The data indicated that myoid hamartoma is a true neoplasm resulting from a mutated mesenchymal stem cell capable of differentiating into smooth muscle cells (23).

We now report the genetic characterization of a leiomyomatous tumor of the breast without evidence of malignancy. We used the above-mentioned methodologies to show that the tumor had an identical genetic profile to that found in the previously examined myoid breast hamartoma. We conclude that a chromosomal translocation t(5;12)(p13;q14) resulting in fusion of *HMGA2* with sequence of chromosome sub-band 5p13.2 is a recurrent genetic event in benign myoid neoplasms of the breast.

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). Written informed consent was obtained from the patient to publication of the case details. The Ethics Committee's approval included a review of the consent procedure. All patient information has been de-identified.

Tumor description. The surgical specimen was from the left breast of a 45-year-old woman. The tumor measured 22×15×20 mm. Its cut surface was white with a whirling pattern and firm texture (Figure 1A). The tumor was well demarcated from the surrounding tissue. Representative areas were selected for further histopathological and cytogenetic analysis. Microscopically, the tumor was composed of bundles of spindle cells without atypia (Figure 1B-D). No infiltration was seen at tumor margins, nor were mitotic activity or necrotic areas found. The tumor cells were positive for smooth muscle actin (Figure 1E), caldesmon (Figure 1F), desmin (Figure 1G), estrogen receptor and progesterone receptor. Staining for cytokeratins and S-100 were negative. Based on these findings, the final pathology report concluded that the tumor was leiomyomatous without any evidence of malignancy.

G-Banding and karyotyping. A part of the resected specimen was received and processed for cytogenetic analysis as previously described (23). The tumor was minced with scalpels into 1-2 mm fragments and then enzymatically disaggregated with collagenase II (Worthington, Freehold, NJ, USA). Dividing cells were cultured, harvested, and examined cytogenetically. For G-banding of chromosome preparations, Wright's stain (Sigma-Aldrich; St Louis, MO, USA) was used. Metaphases were analyzed and karyograms prepared using the CytoVision computer-assisted karyotyping system (Leica Biosystems, Newcastle upon Tyne, UK). The karyotypes were described according to the International System for Human Cytogenomic Nomenclature (26).

FISH. FISH analysis was performed on both metaphase plates and interphase nuclei using an in-house prepared *HMGA2* break-apart probe. The probe was made from commercially available bacterial artificial chromosomes (BAC) purchased from the BACPAC Resource Center operated by BACPAC Genomics, Emeryville, CA, USA (https://bacpacresources.org/) (Table I). The FISH probes were prepared from bacteriophage Phi29 DNA polymerase-amplified BAC DNAs using previously described methodology (27) and kits for DNA isolation, amplification, labelling, and hybridization according to the manufacturers' recommendations. In brief, single isolated bacterial colonies were grown in 5 ml culture overnight and BAC DNA was purified from them using High Pure Plasmid Isolation Kit (Roche Diagnostics, Mannheim, Germany). Following purification, BAC DNAs were isothermally amplified with Phi29 DNA polymerase using a GenomiPhi V2 DNA Amplification Kit (Cytiva, Marlborough, MA, USA). Finally, amplified BAC DNAs were labelled and hybridized using a nick translation kit (Abbott Molecular, Des Plaines, IL, USA).

All the BAC clones map to chromosome sub-band 12q14.3 and cover the *HMGA2* locus (Table I). The proximal to centromere part of the probe was constructed from a pool of clones RP11-185K16, RP11-30I11, and RP11-662G15 and labelled with Texas Red-5-dCTP (PerkinElmer, Boston, MA, USA) to obtain a red signal. The distal to centromere part of the probe was constructed from a pool of clones RP11-118B13, RP11-745O10, and RP11-263A04 and labelled with fluorescein-12-dCTP (PerkinElmer) to obtain a green signal. Chromosome preparations were counterstained with 0.2 μg/ml 4',6-diamidino-2-phenylindole 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 using miRNeasy Mini Kit (Qiagen, Hilden, Germany) from a frozen (−80˚C) part of the tumor specimen adjacent to where material had been taken for cytogenetic analysis and histological examination. Two hundred nanograms of total RNA was sent to the Genomics Core Facility at the Norwegian Radium Hospital, Oslo University Hospital, for high-throughput paired-end RNA-sequencing and a total of $185×10^6$ 101-bp-length-reads were obtained. FASTQC software was used for quality control of the raw sequence data (available online at: http://www.bioinformatics.babraham.ac.uk/projects/fastqc/). The software deFuse was used for detection of possible *HMGA2* fusion transcripts (28).

RT-PCR and Sanger sequencing analyses. In order to confirm the existence of an *HMGA2* fusion with sequences from chromosome band 5p13, RT-PCR and Sanger sequencing analyses were performed. cDNA was synthesized from 1 μg of total RNA 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). Then cDNA corresponding to 20 ng total RNA was used as template in a 25-μl reaction volume PCR assay containing 12.5 μl Premix Ex Taq™ DNA Polymerase Hot Start

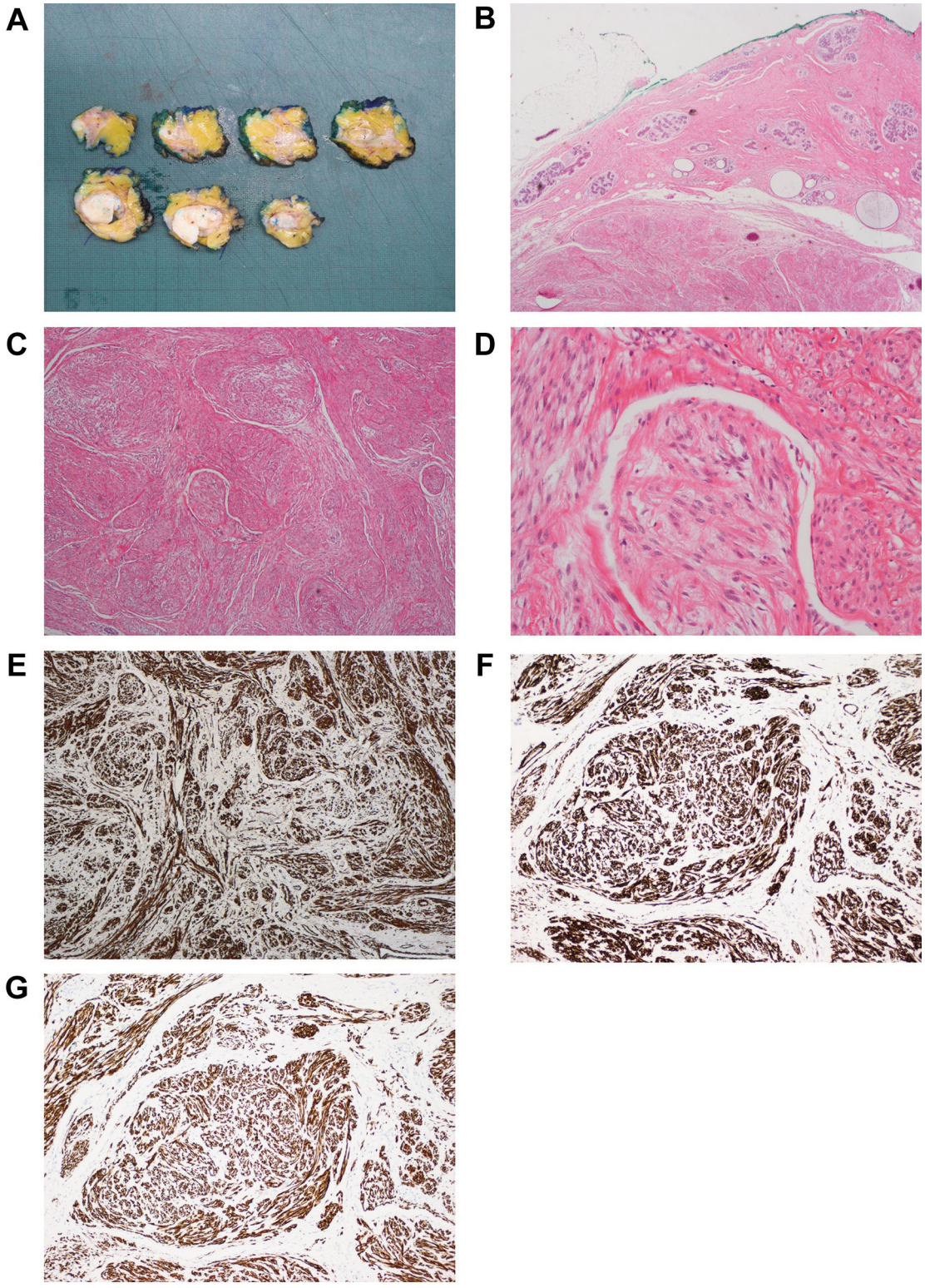

Figure 1. *Pathological examination of the mammary leiomyomatous tumor. A: Macroscopic image of the tumor with surrounding tissue. B: Hematoxylin and eosin (H&E)-stained section showing a well-demarcated tumor (lower part) facing normal breast tissue, ×20. C: H&E-stained section showing bundles of smooth muscle without atypia against a collagen-rich background, ×40. D: The H&E-stained section of C shown at higher magnification ×200. E: Immunohistochemical staining for smooth muscle actin, highlighting smooth muscle cells, ×40. F: Immunohistochemical staining for caldesmon, ×100. G: Immunohistochemical staining with desmin, ×100.*

Table I. *Bacterial artificial chromosomes (BAC) probes used for fluorescence in situ hybridization experiments in order to detect rearrangement of high-mobility group AT-hook 2 (HMGA2) gene. The position of HMGA2 (NM_003483.6) is also given.*

BAC clone	Accession number	Chr mapping	Position on GRCh38/ hg38 assembly	Labeling
RP11-185K16	AQ418927.1 and AQ418930.1	12q14.3	Chr12:65427017-65594623	Texas Red-5-dCTP (Red)
RP11-30I11	B87811.1 and B87812.1	12q14.3	Chr12:65498459-65669659	Texas Red-5-dCTP (Red)
RP11-662 G15	AQ411650 and AQ411760	12q14.3	Chr12:65608717-65818177	Texas Red-5-dCTP (Red)
	NM_003483.6	12q14.3	Chr12:65824483-65966291	
RP11-118B13	AQ347872.1, AQ347869.1, and AC135255.2	12q14.3	Chr12:65964922-66109206	Fluorescein-12-dCTP (Green)
RP11-745O10	AC078927.20	12q14.3	Chr12:66083023-66208799	Fluorescein-12-dCTP (Green)
RP11-263A04	AC025603.1	12q14.3	Chr12:66246378-66412442	Fluorescein-12-dCTP (Green)

Chr: Chromosome.

Version (Takara Bio Europe/SAS, Saint-Germain-en-Laye, France) and 0.4 μM of each of the forward and reverse primers. The primers used were the same as those in our previous study of myoid hamartoma of the breast (23), namely a forward primer HMGA2-929F1: ACCGGTGAGCCCTCTCCTAAGAG (reference sequence: NM_003483.4, position: 929-951) and a reverse primer 5p13R: GAAATGGGTCAGGCCTATCAGCA (reference sequence: AC027347.5, position: 115124-115102). As a positive control for PCR amplification, synthesized cDNA from the previously published case of myoid hamartoma was used (23).

A C-1000 Thermal cycler (Bio-Rad) was used for PCR amplification. The cycling profile was 30 s at 94˚C followed by 35 cycles of 7 s at 98˚C, 30 s at 60˚C, 30 s at 72˚C, and a final extension step for 5 min at 72˚C. Three microliters of the PCR products were stained with GelRed (Biotium, Fremont, CA, USA), analyzed by electrophoresis through 1.0 % agarose gel, and photographed. The remaining PCR products were purified using a MinElute PCR Purification Kit (Qiagen) and Sanger-sequenced with the dideoxy procedure using a BigDye Direct Cycle Sequencing Kit following the company's recommendations (ThermoFisher Scientific, Waltham, MA, USA). The primers used for sequencing were the same as above containing M13 forward and M13 reverse primer sequences at their 5´-end: M13-forward-HMGA2-929F1: TGTAAAACGACGGCCAGT-ACCGGTGAGCCCTCTCCTAAGAG and M13-reverse-5p13R: CAGGAAACAGCTATGACC-GAAATGGGTCAGGCCTATC AGCA. Sequencing was run on an Applied Biosystems SeqStudio Genetic Analyzer system (ThermoFisher Scientific).

The Basic Local Alignment Search Tool (BLAST) was used to compare the sequences obtained by Sanger sequencing with reference sequences NM_003483.4 (*HMGA2*) and AC027347.5 (sub-band 5p13.2) (29). The BLAST-like alignment tool (BLAT) and the human genome browser were also used to map the sequences on the Human GRCh37/hg19 assembly (30).

Results

The G-banding analysis revealed a sole balanced chromosomal translocation in all examined metaphases, yielding the karyotype 46,XX,t(5;12)(p13;q14)[14] (Figure 2A). FISH analysis of metaphase spreads showed rearrangement of the *HMGA2* locus, indicating a genomic breakpoint within the *HMGA2* gene: The distal part of the *HMGA2* probe hybridized to the p13 band of the der(5), whereas the proximal part of the probe hybridized to the q14 band of the der(12) (Figure 2B). FISH analysis of interphase nuclei showed two yellow signals in four nuclei (normal *HMGA2*) whereas one yellow, one red and one green signals (corresponding to splitting of the *HMGA2* probe) were seen in 96 nuclei out of 100 examined nuclei (data not shown).

Analysis of the fastq files of the RNA sequencing data using the software package deFuse detected an *HMGA2* chimeric transcript in which exon 3 of *HMGA2* (nt 1060 in reference sequence with accession number NM_003483.4) was fused with an intragenic sequence from chromosome band 5p13.2 (Figure 3A), position chr5:35,321,780-35,322,072 in GRCh37/hg19 assembly (Figure 3B and C). It mapped approximately 232 kbp upstream from the 5´-end region of the gene that encodes prolactin receptor (*PRLR*) and 296 kbp upstream of the sperm flagellar protein 2 (*SPEF2*) gene (Figure 3B and C). RT-PCR with the primer combination HMGA2-929F1/5p13R amplified a 349-bp cDNA fragment (Figure 3D). Direct sequencing of the PCR fragment showed that it was a *HMGA2*-chimeric cDNA fragment (Figure 3E).

The *HMGA2* fusion transcript found in the present tumor was identical to that we previously reported in a myoid hamartoma of the breast carrying a similar-looking t(5;12)(p13;q14) chromosomal translocation (23). It was predicted to code for a putative peptide containing amino acid residues 1-83 of HMGA2 protein (accession number NP_003474.1), corresponding to exons 1-3 of the gene, and nine amino acid residues from the sequence from chromosome band 5p13 (ValHisSerThrGlyGluLysGlnSer) (Figure 3E).

Discussion

The present case of leiomyomatous tumor, apart from the identical genetic aberrations, had the same morphology and histology as the myoid hamartoma previously reported by

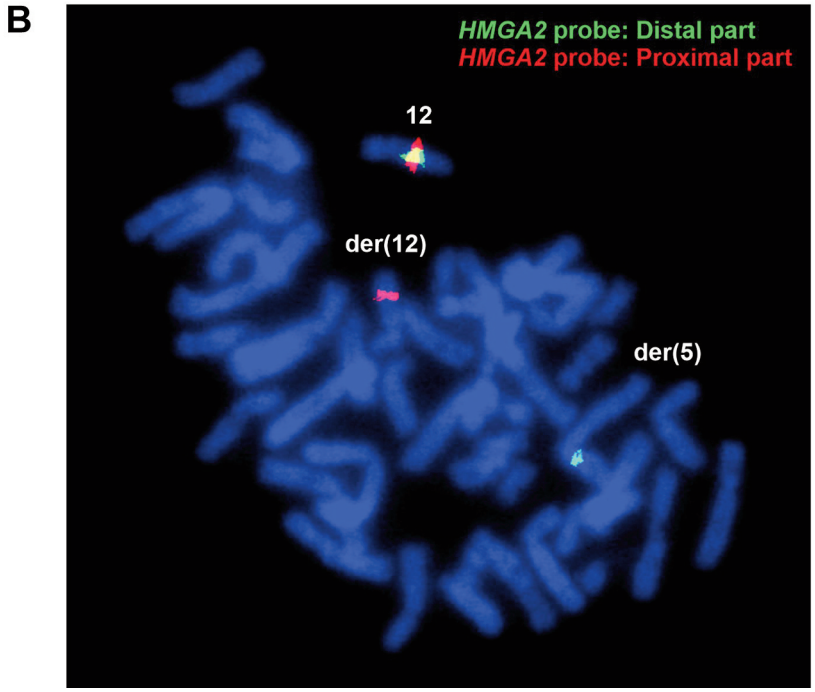

Figure 2. *G-Banding and fluorescence in situ hybridization (FISH) analyses of the mammary leiomyomatous tumor. A: Karyogram showing two abnormal chromosomes, der(5)t(5;12)(p13;q14) and der(12)t(5;12)(p13;q14). Breakpoint positions are indicated by arrows. B: FISH on a metaphase spread with the high-mobility group AT-hook 2 (HMGA2) break-apart probe showing a yellow normal signal on chromosome 12, a red signal on der(12), and a green signal on der(5), suggesting rearrangement of the HMGA2 gene.*

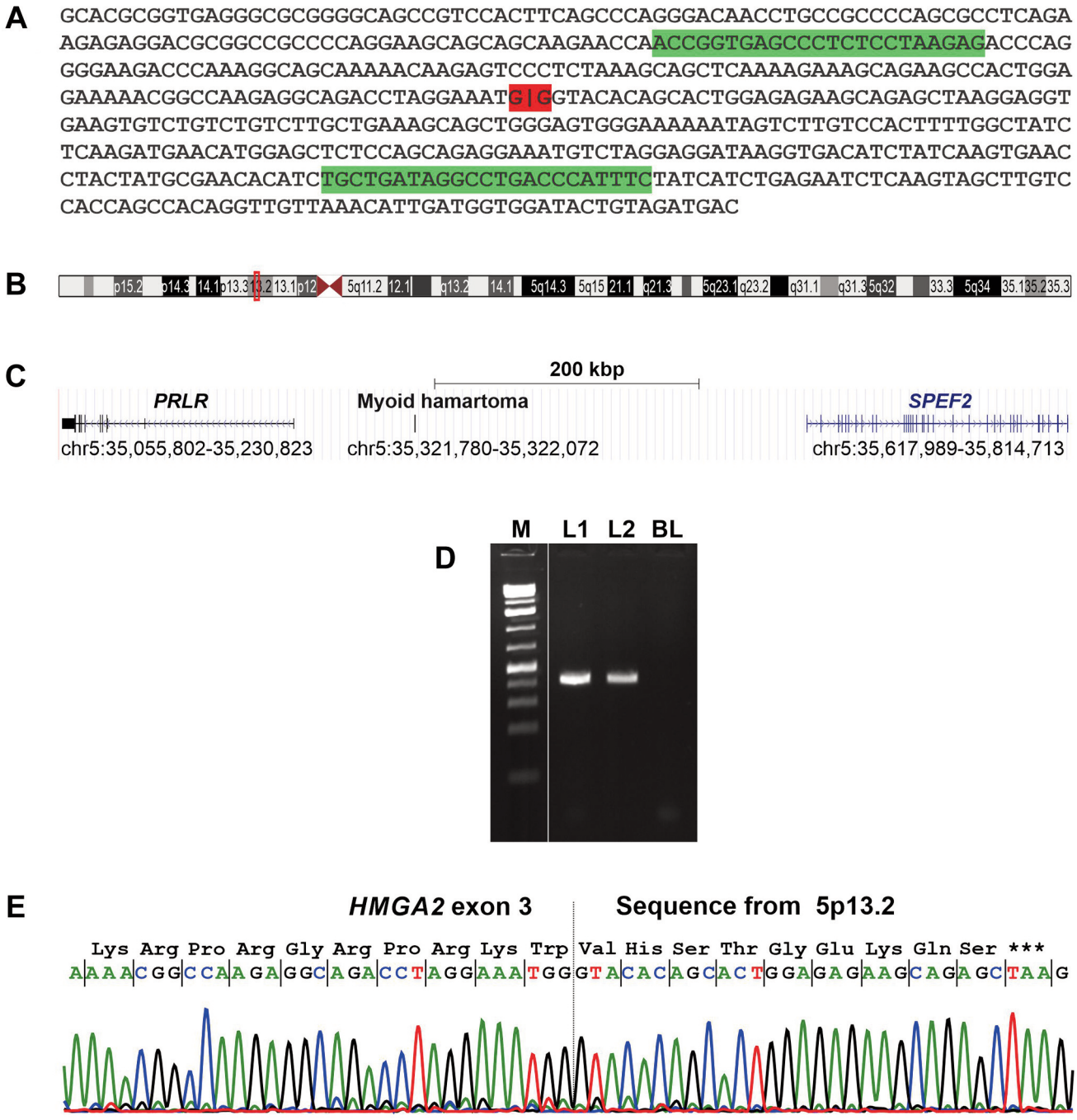

Figure 3. *Molecular genetic examination of the mammary leiomyomatous tumor. A: The high-mobility group AT-hook 2 (HMGA2) fusion sequence was obtained from raw RNA sequencing data using the deFuse software package. The G|G junction of HMGA2 with a sequence from chromosome sub-band 5p13.2 is highlighted in red. The position of the forward HMGA2-929F1 and reverse 5p13R primers are highlighted in green. B: Ideogram of chromosome 5 showing the position of the sequence of myoid hamartoma found by RNA sequencing/deFuse software to have fused with exon 3 of HMGA2, together with the prolactin receptor (PRLR) and sperm flagellar 2 (SPEF2) genes in sub-band 5p13.2 (red box). C: Diagram showing the 768-kbp region of the sub-band 5p13.2 which contained the sequence of myoid hamartoma, PRLR, and SPEF2 together with their genomic positions on the GRCh37/hg19 assembly. D: Gel electrophoresis showing the amplified cDNA fragment using the forward primer HMGA2-929F1 and the reverse 5p13R. M: 1-kb DNA ladder (GeneRuler, ThermoFisher Scientific). L1: The fragment from the positive control (previously published myoid hamartoma). L2: The fragment from the present myoid hamartoma of the breast. BL: Blank, water as template in the polymerase chain reaction. E: Partial sequence chromatograms of the cDNA amplified fragment showing the junction position of HMGA2 and the sequence from chromosome sub-band 5p13.2 (vertical dotted line) together with part of the coding peptide. ***Denotes stop of translation.*

our group (23). In order to make diagnosis of the current lesion, as well as our previously reported case, both myoid hamartoma and leiomyoma were considered.

Leiomyomas are common in some organs, primarily the uterus, but rare in the breast. They may be found either in the nipple-areola complex or in the mammary parenchyma (31-38). Leiomyomas in the former location were first described by Virchow in 1854 and, since then, 50-60 cases have been reported (36, 37). Leiomyomas of mammary parenchyma were first described by Strong in 1913, and approximately 30 cases have since been reported (31, 32, 35, 39), one of them in a male patient (40). Whereas leiomyomas in the nipple-areola complex are thought to arise from the dartoic muscles of the nipple (36, 37), the histogenesis and origin of other breast leiomyomas remains unclear [see (31, 39, 41) and references therein]. Histologically, breast leiomyomas resemble their counterparts in the uterus inasmuch as they are composed of well-circumscribed proliferations of bland smooth muscle cells arranged in tightly intersecting fascicles (22). Breast leiomyoma cells stain positively with antibodies to desmin and smooth muscle actin, which are specific markers of smooth-muscle differentiation (36, 37). Cytoplasmic immunoreactivity for caldesmon was also reported, adding further support to the assumption that the tumors originate from immature smooth muscle cells (34, 38).

The diagnosis of breast leiomyomas was suggested to be restricted to lesions exclusively composed of smooth muscle cells (11, 42). However, as pointed out by D'Alfonso and co-workers, who undertook an in-depth review of the relevant literature (21), many of the reported cases "lacked thorough microscopic descriptions and/or informative histologic images", making meaningful assessment of published data problematic. They further noted that many reports "show a high magnification of lesional cells, but the incorporation of adipocytes or normal breast glandular tissue within these tumors is not clearly addressed in almost all reports reviewed". In one tumor which was presented as a parenchymal leiomyoma, the attached low-magnification image of the tumor showed the presence of both adipose and breast glandular tissue (21, 43). They therefore concluded that at least some reported 'parenchymal leiomyomas' "would be better classified as myofibroblastomas with leiomyomatous differentiation or myoid hamartomas". Of relevance in the context of this differential diagnostic, Tamir and co-workers pointed out that "Breast leiomyomas are referred to as myoid hamartomas in some textbooks of pathology" (41). It seems fair to conclude that at least some degree of phenotypic uncertainty (or even confusion) exists with regard to how leiomyomatous breast tumors should best be classified.

The general histological description of myoid hamartomas of the breast maintains that in this tumor, the smooth muscle component is mixed with other elements such as adipose tissue, fibrous stroma, and glandular tissues (22, 25). Although the presence of both adipose tissue and sclerosing adenosis is considered to be diagnostically important (21), myoid hamartomas with only one of these two features have been reported (7, 11). The immunohistochemical profile of myoid hamartoma is similar to that of leiomyoma. They stain positively for specific markers of smooth-muscle differentiation such as smooth muscle actin, vimentin, desmin, and caldesmon (15, 18, 22, 24, 25), and they are also positive for estrogen and progesterone receptors (15, 18, 22, 24, 25). A similar positivity for estrogen receptors and progesterone receptors has also been found in retroperitoneal-abdominal cavity leiomyomas (44, 45), uterine leiomyomas (46-49), and most breast hamartomas (50, 51).

The smooth muscle component of myoid hamartomas is intriguing because, apart from the erector muscle of the nipple and the vessels, smooth muscle cells are generally absent from normal mammary stroma (13, 21). Thus, in myoid hamartomas, the smooth muscle tumor component was suggested to originate from the myoepithelium through a metaplastic process, or from stromal myofibroblasts, from the walls of local vessels, or from a stem cell capable of multidirectional differentiation (5, 6, 8, 11, 13, 18, 21, 25, 52). In the third and fourth editions of Rosen's Breast Pathology textbook, the authors treat hamartoma and myoid hamartoma as two different lesions, writing about the latter that "Regrettably, the designation of these tumors as hamartomas is now well entrenched in the literature", signaling the opinion that myoid hamartomas may not be true hamartomas (42, 53).

When we consider our genetic findings on the two examined myoid tumors, the present case and the one described previously (23), against the background of the above-mentioned considerations, we see the collected evidence pointing towards the following conclusions: Firstly, the term 'hamartoma' is inappropriate for these two tumors. They both carried acquired changes of their genomes, testifying to the fact that they represent genuine neoplasms, not malformations. Regardless of what they are phenotypically called, they were cytogenetically characterized by a translocation t(5;12)(p13;q14) found to result in generation of a chimeric *HMGA2*-transcript in which exon 3 of *HMGA2* fuses to an intergenic sequence from 5p13.2. The putative translated HMGA2 peptide would contain the first 83 HMGA2 amino acid residues encoding the AT-hook domains (exons 1-3 of *HMGA2*), which bind to the minor groove of adenine-thymine-rich DNA, and nine amino acid residues (ValHisSerThrGlyGluLysGlnSer) from the sequence from the chromosome sub-band 5p13.2.

Secondly, these breast tumors had extensive histological, immunohistological, and genetic similarities to leiomyomas of the breast or, for that matter, of other tissues and organs. Small phenotypic differences such as "exclusively composed of smooth muscle cells" should not be seen as an adequate

criterion to define breast leiomyomas and myoid hamartoma as distinct types of neoplasia. Thirdly, the smooth muscle cells probably originate from mesenchymal stem cells capable for osteogenic, chondrogenic, adipogenic, and myogenic differentiation (54). Adipose-derived mesenchymal stem cells (ADSCs) have been isolated from breast tissue (55-57). ADSCs from various sources, including breast tissue, were shown to differentiate *in vitro* into adipogenic, chondrogenic, myogenic, and osteogenic cells when subjected to culture conditions known to facilitate growth along these respective axes of development (55, 58-60). Thus, the smooth muscle components together with chondroid differentiation found in myoid hamartomas of breast with chondroid metaplasia (14, 18, 20) might be explained by differentiation of ADSCs into myogenic and chondrogenic cells.

The pattern of acquired genetic aberrations seen in this tumor and the previous one (23) is in one sense unique inasmuch as t(5;12)(p13;q14) has not been described in leiomyomas before (61). At the same time, however, it nevertheless involves the same pathogenetic theme that is so commonly operative in many other benign connective tissue tumors, not least leiomyomas, inasmuch as *HMGA2* was found to be rearranged. Typically, a translocation-mediated disruption of the *HMGA2* locus separates exons 1-3 or 1-4, coding the three AT-hook DNA binding domains, from the 3´-untranslated region of the gene which normally regulates *HMGA2* transcription (62-66). The importance of a truncated form of *HMGA2* in neoplastic transformation is also underpinned by results obtained *in vitro* (67-72). Thus, a truncated form of HMGA2 protein carrying only the three AT-hook DNA-binding domains transformed mouse embryonic fibroblasts (NIH3T3 cells) (67). Overexpression of the truncated form of *HMGA2* in human myometrial cells resulted in the formation of leiomyoma-like tissue (73). A synthetic peptide comprising the AT-hook motifs of the HMGA2 protein promoted *in vitro* proliferation of porcine hyaline cartilage chondrocytes (71). In transgenic mice, expression of the truncated form of *HMGA2* under control of the H2-K1 promoter (official name histocompatibility 2, K1, K region) resulted in development of lipomas (68). In another model, expression of full-length *HMGA2* under the control of the powerful cytomegalovirus promoter led to the development of mixed growth hormone/prolactin cell pituitary adenomas (69). In yet another model, expression of truncated human *HMGA2* transcripts in transgenic mice under transcriptional control of the promoter of murine fatty acid-binding protein 4 gene resulted in the development of several neoplasms, including fibroadenomas of the breast and salivary gland adenomas (70). Finally, in knockout mice, *HMGA2* was found to regulate insulin-like growth factor 2 mRNA-binding protein 2 and be a key regulator of myoblast proliferation and myogenesis (72). *Hmga2* knockout mice had reduced myoblast proliferation and deficient muscle growth, whereas overexpression of *Hmga2* promoted myoblast growth (72).

Previous cytogenetic information on mammary hamartomas is restricted to only four cases (74-76). Dietrich and co-workers (74) reported the cytogenetic analysis of two breast hamartomas (referred to as adenolipomas in their study), one with the karyotype, 47,XX,+del(1)(p22), the second with 46,XX,t(12;16)(q15;q24) (74). By culturing mesenchymal and epithelial cells separately by using different media, they showed that the cells harboring the t(12;16)(q15;q24) chromosomal aberrations were of mesenchymal origin, whereas the epithelial elements had normal karyotype. Rohen and co-workers reported a breast hamartoma with a predominance (80%) of mature adipose cells with the following karyotype: 46,XX,add(4)(?),add(6)(q?),der(7)t(7;12)(q11;q11-12),der(12). They also showed that the breakpoint on 12q was within the same region as similar breakpoints found in many other benign solid tumors, such as uterine leiomyoma, lipoma, and pleomorphic salivary gland adenomas (75). The fourth breast hamartoma, lacking fat, cartilage or smooth muscle cell differentiation, had the karyotype 46,XX,t(1;6)(p21;p21) with rearrangement of *HMGA1* on 6p21 (76). Lineage-specific clonal cytogenetic aberrations have also been found in breast fibroadenomas, pulmonary chondroid hamartomas, and endometrial polyp (77-79); in all of them where information is available, the mesenchymal component was the one carrying chromosomal aberrations (77-79). Fletcher and co-workers expressed the view that the lineage-specific cytogenetic abnormalities in pulmonary chondroid hamartomas supported the redesignation of such tumors as pulmonary chondromas (77).

In conclusion, we show that the chromosomal translocation t(5;12)(p13;q14) resulting in fusion of *HMGA2* with sequences from sub-band 5p13.2 is a consistent genetic event in benign myoid neoplasms of the breast. The finding indicates that what has been called myoid hamartoma is a true neoplasm of the breast, not a malformation. In all likelihood, the tumor stems from a mutated (in the sense that it has acquired a tumorigenic genomic rearrangement) mesenchymal stem cell capable of differentiating into smooth muscle cells.

Conflicts of Interest

The Authors declare that they have no potential conflicts of interest exist.

Authors' Contributions

IP designed and supervised the research, performed RT-PCR and Sanger sequencing analyses and bioinformatics analysis, and wrote the article. LG performed cytogenetic analysis and evaluated the FISH data. KA performed RT-PCR and Sanger sequencing analyses, FISH analysis, and evaluated the data. ML-I, HRH and IL performed the pathological examination. FM interpreted the data. SH assisted with G-banding, karyotyping, FISH and writing of the article. All Authors read and approved the final article.

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References

1 Leiter Herrán F, Restrepo CS, Alvarez Gómez DI, Suby-Long T, Ocazionez D and Vargas D: Hamartomas from head to toe: an imaging overview. Br J Radiol *90(1071)*: 20160607, 2017. PMID: 27936889. DOI: 10.1259/bjr.20160607

2 Ali SA and Mulita F: Hamartoma. In: StatPearls. Treasure Island, FL, USA, 2022.

3 Ober WB: Selected items from the history of pathology: Eugen Albrecht, MD (1872-1908): hamartoma and choristoma. Am J Pathol *91(3)*: 606, 1978. PMID: 350057.

4 Arrigoni MG, Dockerty MB and Judd ES: The identification and treatment of mammary hamartoma. Surg Gynecol Obstet *133(4)*: 577-582, 1971. PMID: 5096305.

5 Davies JD and Riddell RH: Muscular hamartomas of the breast. J Pathol *111(3)*: 209-211, 1973. PMID: 4128204. DOI: 10.1002/path.1711110309

6 Eusebi V, Cunsolo A, Fedeli F, Severi B and Scarani P: Benign smooth muscle cell metaplasia in breast. Tumori *66(5)*: 643-653, 1980. PMID: 7466927.

7 Huntrakoon M and Lin F: Muscular hamartoma of the breast. An electron microscopic study. Virchows Arch A Pathol Anat Histopathol *403(3)*: 307-312, 1984. PMID: 6428044. DOI: 10.1007/BF00694907

8 Daroca PJ Jr, Reed RJ, Love GL and Kraus SD: Myoid hamartomas of the breast. Hum Pathol *16(3)*: 212-219, 1985. PMID: 3972402. DOI: 10.1016/s0046-8177(85)80004-6

9 Garfein CF, Aulicino MR, Leytin A, Drossman S, Hermann G and Bleiweiss IJ: Epithelioid cells in myoid hamartoma of the breast: a potential diagnostic pitfall for core biopsies. Arch Pathol Lab Med *120(7)*: 676-680, 1996. PMID: 8757475.

10 Rosser RJ: Epithelioid cells in myoid hamartoma of the breast. Arch Pathol Lab Med *121(4)*: 354-355, 1997. PMID: 9140300.

11 Magro G and Bisceglia M: Muscular hamartoma of the breast. Case report and review of the literature. Pathol Res Pract *194(5)*: 349-355, 1998. PMID: 9651948. DOI: 10.1016/s0344-0338(98)80059-9

12 Murugesan JR, Joglekar S, Valerio D, Bradley S, Clark D and Jibril JA: Myoid hamartoma of the breast: case report and review of the literature. Clin Breast Cancer *7(4)*: 345-346, 2006. PMID: 17092405. DOI: 10.3816/CBC.2006.n.050

13 Stafyla V, Kotsifopoulos N, Grigoriadis K, Bakoyiannis CN, Peros G and Sakorafas GH: Myoid hamartoma of the breast: a case report and review of the literature. Breast J *13(1)*: 85-87, 2007. PMID: 17214800. DOI: 10.1111/j.1524-4741.2006.00369.x

14 Khoo JJ, Alwi RI and Abd-Rahman I: Myoid hamartoma of breast with chondroid metaplasia: a case report. Malays J Pathol *31(1)*: 77-80, 2009. PMID: 19694319.

15 Kajo K, Zubor P and Danko J: Myoid (muscular) hamartoma of the breast: case report and review of the literature. Breast Care (Basel) *5(5)*: 331-334, 2010. PMID: 21779216. DOI: 10.1159/000321341

16 Ko MS, Jung WS, Cha ES and Choi HJ: A rare case of recurrent myoid hamartoma mimicking malignancy: imaging appearances. Korean J Radiol *11(6)*: 683-686, 2010. PMID: 21076595. DOI: 10.3348/kjr.2010.11.6.683

17 Mizuta N, Sakaguchi K, Mizuta M, Imai A, Nakatsukasa K, Morita M, Soshi M, Goto M, Yasukawa S, Konishi E and Taguchi T: Myoid hamartoma of the breast that proved difficult to diagnose: a case report. World J Surg Oncol *10*: 12, 2012. PMID: 22248347. DOI: 10.1186/1477-7819-10-12

18 Nasit JG, Parikh B, Trivedi P and Shah M: Myoid (muscular) hamartoma of the breast with chondroid metaplasia. Indian J Pathol Microbiol *55(1)*: 121-122, 2012. PMID: 22499322. DOI: 10.4103/0377-4929.94883

19 Schäfer FK, Biernath-Wuepping J, Eckmann-Scholz C, Order BM, Mathiak M, Hilpert F, Strauss A, Jonat W and Schäfer PJ: Rare benign entities of the breast – myoid hamartoma and capillary hemangioma. Geburtshilfe Frauenheilkd *72(5)*: 412-418, 2012. PMID: 25298546. DOI: 10.1055/s-0031-1298571

20 Su CC, Chen CJ, Kuo SJ and Chen DR: Myoid hamartoma of the breast with focal chondromyoxid metaplasia and pseudoangiomatous stromal hyperplasia: A case report. Oncol Lett *9(4)*: 1787-1789, 2015. PMID: 25789043. DOI: 10.3892/ol.2015.2892

21 D'Alfonso TM, Subramaniyam S, Ginter PS, Mosquera JM, MacDonald TY, Noorzad Z, Orta LY, Liu YF, Rubin MA and Shin SJ: Characterization of the leiomyomatous variant of myofibroblastoma: a rare subset distinct from other smooth muscle tumors of the breast. Hum Pathol *58*: 54-61, 2016. PMID: 27498061. DOI: 10.1016/j.humpath.2016.07.018

22 Krings G, McIntire P and Shin SJ: Myofibroblastic, fibroblastic and myoid lesions of the breast. Semin Diagn Pathol *34(5)*: 427-437, 2017. PMID: 28751104. DOI: 10.1053/j.semdp.2017.05.010

23 Panagopoulos I, Gorunova L, Andersen HK, Pedersen TD, Lømo J, Lund-Iversen M, Micci F and Heim S: Genetic characterization of myoid hamartoma of the breast. Cancer Genomics Proteomics *16(6)*: 563-568, 2019. PMID: 31659109. DOI: 10.21873/cgp.20158

24 Xia T, Qin C, Long H, Zhou T and Xiao X: Mammary myoid hamartomas: reports of two cases and a review of the literature. Int J Clin Exp Pathol *12(7)*: 2398-2404, 2019. PMID: 31934067.

25 Kim N, Park M and Lee J: Myoid hamartoma of the breast: a case report. Journal of Breast Disease *8(2)*: 129-133, 2021. DOI: 10.14449/jbd.2020.8.2.129

26 McGowan-Jordan J, Hastings RJ and Moore S: ISCN 2020: An International System for Human Cytogenomic Nomenclature. Basel, Karger, pp. 170, 2020.

27 Roohi J, Cammer M, Montagna C and Hatchwell E: An improved method for generating BAC DNA suitable for FISH. Cytogenet Genome Res *121(1)*: 7-9, 2008. PMID: 18544919. DOI: 10.1159/000124374

28 McPherson A, Hormozdiari F, Zayed A, Giuliany R, Ha G, Sun MG, Griffith M, Heravi Moussavi A, Senz J, Melnyk N, Pacheco 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

29 Altschul SF, Gish W, Miller W, Myers EW and Lipman DJ: Basic local alignment search tool. J Mol Biol *215(3)*: 403-410, 1990. PMID: 2231712. DOI: 10.1016/S0022-2836(05)80360-2

30 Kent WJ: BLAT – the BLAST-like alignment tool. Genome Res *12(4)*: 656-664, 2002. PMID: 11932250. DOI: 10.1101/gr.229202

31 Diaz-Arias AA, Hurt MA, Loy TS, Seeger RM and Bickel JT: Leiomyoma of the breast. Hum Pathol *20(4)*: 396-399, 1989. PMID: 2467872. DOI: 10.1016/0046-8177(89)90052-x

32 Kaufman HL and Hirsch EF: Leiomyoma of the breast. J Surg Oncol *62(1)*: 62-64, 1996. PMID: 8618404. DOI: 10.1002/(SICI)1096-9098(199605)62:1<62::AID-JSO13>3.0.CO;2-V

33 Pourbagher A, Pourbagher MA, Bal N, Oguzkurt L and Ezer A: Leiomyoma of the breast parenchyma. AJR Am J Roentgenol *185(6)*: 1595-1597, 2005. PMID: 16304020. DOI: 10.2214/AJR.04.1453

34 Kafadar MT, Yalçın M, Gök MA, Aktaş A, Yürekli TS and Arslan Aİ: Intraparenchymal leiomyoma of the breast: a rare location for an infrequent tumor. Eur J Breast Health *13(3)*: 156-158, 2017. PMID: 28894856. DOI: 10.5152/ejbh.2017.3472

35 Brandão RG, Elias S, Pinto Nazário AC, Alcoforado Assunção MDCG, Esposito Papa CC and Facina G: Leiomyoma of the breast parenchyma: a case report and review of the literature. Sao Paulo Med J *136(2)*: 177-181, 2017. PMID: 28977094. DOI: 10.1590/1516-3180.2016.0253040117

36 Hammer P, White K, Mengden S, Korcheva V and Raess PW: Nipple leiomyoma: A rare neoplasm with a broad spectrum of histologic appearances. J Cutan Pathol *46(5)*: 343-346, 2019. PMID: 30663114. DOI: 10.1111/cup.13423

37 Salemis NS: Subareolar male genital leiomyoma: An exceedingly rare clinical entity. Breast J *26(11)*: 2248-2249, 2020. PMID: 32935434. DOI: 10.1111/tbj.14052

38 Zhong E, Swistel A, Viswanathan K and Hoda SA: Leiomyoma of the Nipple: A common neoplasm in an uncommon location. Breast J *26(3)*: 529-530, 2020. PMID: 31486152. DOI: 10.1111/tbj.13572

39 Minami S, Matsuo S, Azuma T, Uga T, Hayashi T, Eguchi S and Kanematsu T: Parenchymal leiomyoma of the breast: a case report with special reference to magnetic resonance imaging findings and an update review of literature. Breast Cancer *18(3)*: 231-236, 2011. PMID: 21416339. DOI: 10.1007/s12282-011-0257-6

40 Strader LA, Galan K and Tenofsky PL: Intraparenchymal leiomyoma of the male breast. Breast J *19(6)*: 675-676, 2013. PMID: 24102921. DOI: 10.1111/tbj.12190

41 Tamir G, Yampolsky I and Sandbank J: Parenchymal leiomyoma of the breast. Report of a case and clinicopathological review. Eur J Surg Oncol *21(1)*: 88-89, 1995. PMID: 7851564. DOI: 10.1016/s0748-7983(05)80077-0

42 Hoda SA, Brogi E, Koerner F and Rosen PP: Rosen's Breast Pathology. Fourth Edition. Lippincott Williams & Wilkins, 2014.

43 Granic M, Stefanovic-Radovic M, Zdravkovic D, Ivanovic N, Nikolic D, Radovanovic D and Stojiljkovic M: Intraparenchimal leiomyoma of the breast. Arch Iran Med *18(9)*: 608-612, 2015. PMID: 26317604.

44 Billings SD, Folpe AL and Weiss SW: Do leiomyomas of deep soft tissue exist? An analysis of highly differentiated smooth muscle tumors of deep soft tissue supporting two distinct subtypes. Am J Surg Pathol *25(9)*: 1134-1142, 2001. PMID: 11688572. DOI: 10.1097/00000478-200109000-00003

45 Panagopoulos I, Gorunova L, Brunetti M, Agostini A, Andersen HK, Lobmaier I, Bjerkehagen B and Heim S: Genetic heterogeneity in leiomyomas of deep soft tissue. Oncotarget *8(30)*: 48769-48781, 2017. PMID: 28591699. DOI: 10.18632/oncotarget.17953

46 Nisolle M, Gillerot S, Casanas-Roux F, Squifflet J, Berliere M and Donnez J: Immunohistochemical study of the proliferation index, oestrogen receptors and progesterone receptors A and B in leiomyomata and normal myometrium during the menstrual cycle and under gonadotrophin-releasing hormone agonist therapy. Hum Reprod *14(11)*: 2844-2850, 1999. PMID: 10548634. DOI: 10.1093/humrep/14.11.2844

47 Jakimiuk AJ, Bogusiewicz M, Tarkowski R, Dziduch P, Adamiak A, Wróbel A, Haczyński J, Magoffin DA and Jakowicki JA: Estrogen receptor alpha and beta expression in uterine leiomyomas from premenopausal women. Fertil Steril *82(Suppl 3)*: 1244-1249, 2004. PMID: 15474102. DOI: 10.1016/j.fertnstert.2004.02.130

48 Bakas P, Liapis A, Vlahopoulos S, Giner M, Logotheti S, Creatsas G, Meligova AK, Alexis MN and Zoumpourlis V: Estrogen receptor alpha and beta in uterine fibroids: a basis for altered estrogen responsiveness. Fertil Steril *90(5)*: 1878-1885, 2008. PMID: 18166184. DOI: 10.1016/j.fertnstert.2007.09.019

49 Tsigkou A, Reis FM, Lee MH, Jiang B, Tosti C, Centini G, Shen FR, Chen YG and Petraglia F: Increased progesterone receptor expression in uterine leiomyoma: correlation with age, number of leiomyomas, and clinical symptoms. Fertil Steril *104(1)*: 170-5.e1, 2015. PMID: 26006736. DOI: 10.1016/j.fertnstert.2015.04.024

50 Herbert M, Sandbank J, Liokumovich P, Yanai O, Pappo I, Karni T and Segal M: Breast hamartomas: clinicopathological and immunohistochemical studies of 24 cases. Histopathology *41(1)*: 30-34, 2002. PMID: 12121234. DOI: 10.1046/j.1365-2559.2002.01429.x

51 Alran L, Chamming's F, Auriol-Leizagoyen S, Velasco V, Deleau F, Brouste V, Bonhomme B, Ben Rejeb H, Marty M and MacGrogan G: Breast hamartoma: reassessment of an under-recognised breast lesion. Histopathology *80(2)*: 304-313, 2022. PMID: 34403159. DOI: 10.1111/his.14544

52 Magro G, Bisceglia M, Michal M and Eusebi V: Spindle cell lipoma-like tumor, solitary fibrous tumor and myofibroblastoma of the breast: a clinico-pathological analysis of 13 cases in favor of a unifying histogenetic concept. Virchows Arch *440(3)*: 249-260, 2002. PMID: 11889594. DOI: 10.1007/s00428-001-0572-y

53 Rosen PP: Rosen's Breast Pathology. Third Edition. Lippincott Williams & Wilkins, 2009.

54 Almalki SG and Agrawal DK: Key transcription factors in the differentiation of mesenchymal stem cells. Differentiation *92(1-2)*: 41-51, 2016. PMID: 27012163. DOI: 10.1016/j.diff.2016.02.005

55 Hanson SE, Kim J and Hematti P: Comparative analysis of adipose-derived mesenchymal stem cells isolated from abdominal and breast tissue. Aesthet Surg J *33(6)*: 888-898, 2013. PMID: 23908304. DOI: 10.1177/1090820X13496115

56 Guneta V, Tan NS, Sugii S, Lim TC, Wong TC and Choong C: Comparative study of adipose-derived stem cells from abdomen and breast. Ann Plast Surg *76(5)*: 569-575, 2016. PMID: 27070348. DOI: 10.1097/SAP.0000000000000797

57 Weigand A, Boos AM, Tasbihi K, Beier JP, Dalton PD, Schrauder M, Horch RE, Beckmann MW, Strissel PL and Strick R: Selective isolation and characterization of primary cells from normal breast and tumors reveal plasticity of adipose derived stem cells. Breast Cancer Res *18(1)*: 32, 2016. PMID: 26968831. DOI: 10.1186/s13058-016-0688-2

58 Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, Alfonso ZC, Fraser JK, Benhaim P and Hedrick MH: Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell *13(12)*: 4279-4295, 2002. PMID: 12475952. DOI: 10.1091/mbc.e02-02-0105

59 Stern-Straeter J, Bonaterra GA, Juritz S, Birk R, Goessler UR, Bieback K, Bugert P, Schultz J, Hörmann K, Kinscherf R and Faber A: Evaluation of the effects of different culture media on the myogenic differentiation potential of adipose tissue- or bone

marrow-derived human mesenchymal stem cells. Int J Mol Med *33(1)*: 160-170, 2014. PMID: 24220225. DOI: 10.3892/ijmm.2013.1555

60 Forcales SV: Potential of adipose-derived stem cells in muscular regenerative therapies. Front Aging Neurosci *7*: 123, 2015. PMID: 26217219. DOI: 10.3389/fnagi.2015.00123

61 Mitelman F, Johansson B and Mertens F: Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer, 2022. Available at: https://mitelmandatabase.isb-cgc.org [Last accessed on April 25, 2022]

62 Borrmann L, Wilkening S and Bullerdiek J: The expression of HMGA genes is regulated by their 3'UTR. Oncogene *20(33)*: 4537-4541, 2001. PMID: 11494149. DOI: 10.1038/sj.onc.1204577

63 Lee YS and Dutta A: The tumor suppressor microRNA let-7 represses the HMGA2 oncogene. Genes Dev *21(9)*: 1025-1030, 2007. PMID: 17437991. DOI: 10.1101/gad.1540407

64 Mayr C, Hemann MT and Bartel DP: Disrupting the pairing between let-7 and Hmga2 enhances oncogenic transformation. Science *315(5818)*: 1576-1579, 2007. PMID: 17322030. DOI: 10.1126/science.1137999

65 Klemke M, Meyer A, Hashemi Nezhad M, Belge G, Bartnitzke S and Bullerdiek J: Loss of let-7 binding sites resulting from truncations of the 3' untranslated region of HMGA2 mRNA in uterine leiomyomas. Cancer Genet Cytogenet *196(2)*: 119-123, 2010. PMID: 20082846. DOI: 10.1016/j.cancergencyto.2009.09.021

66 Kristjánsdóttir K, Fogarty EA and Grimson A: Systematic analysis of the Hmga2 3' UTR identifies many independent regulatory sequences and a novel interaction between distal sites. RNA *21(7)*: 1346-1360, 2015. PMID: 25999317. DOI: 10.1261/rna.051177.115

67 Fedele M, Berlingieri MT, Scala S, Chiariotti L, Viglietto G, Rippel V, Bullerdiek J, Santoro M and Fusco A: Truncated and chimeric HMGI-C genes induce neoplastic transformation of NIH3T3 murine fibroblasts. Oncogene *17(4)*: 413-418, 1998. PMID: 9696033. DOI: 10.1038/sj.onc.1201952

68 Arlotta P, Tai AK, Manfioletti G, Clifford C, Jay G and Ono SJ: Transgenic mice expressing a truncated form of the high mobility group I-C protein develop adiposity and an abnormally high prevalence of lipomas. J Biol Chem *275(19)*: 14394-14400, 2000. PMID: 10747931. DOI: 10.1074/jbc.m000564200

69 Fedele M, Battista S, Kenyon L, Baldassarre G, Fidanza V, Klein-Szanto AJ, Parlow AF, Visone R, Pierantoni GM, Outwater E, Santoro M, Croce CM and Fusco A: Overexpression of the HMGA2 gene in transgenic mice leads to the onset of pituitary adenomas. Oncogene *21(20)*: 3190-3198, 2002. PMID: 12082634. DOI: 10.1038/sj.onc.1205428

70 Zaidi MR, Okada Y and Chada KK: Misexpression of full-length HMGA2 induces benign mesenchymal tumors in mice. Cancer Res *66(15)*: 7453-7459, 2006. PMID: 16885341. DOI: 10.1158/0008-5472.CAN-06-0931

71 Richter A, Lübbing M, Frank HG, Nolte I, Bullerdiek JC and von Ahsen I: High-mobility group protein HMGA2-derived fragments stimulate the proliferation of chondrocytes and adipose tissue-derived stem cells. Eur Cell Mater *21*: 355-363, 2011. PMID: 21484705. DOI: 10.22203/ecm.v021a26

72 Li Z, Gilbert JA, Zhang Y, Zhang M, Qiu Q, Ramanujan K, Shavlakadze T, Eash JK, Scaramozza A, Goddeeris MM, Kirsch DG, Campbell KP, Brack AS and Glass DJ: An HMGA2-IGF2BP2 axis regulates myoblast proliferation and myogenesis. Dev Cell *23(6)*: 1176-1188, 2012. PMID: 23177649. DOI: 10.1016/j.devcel.2012.10.019

73 Mas A, Cervelló I, Fernández-Álvarez A, Faus A, Díaz A, Burgués O, Casado M and Simón C: Overexpression of the truncated form of High Mobility Group A proteins (HMGA2) in human myometrial cells induces leiomyoma-like tissue formation. Mol Hum Reprod *21(4)*: 330-338, 2015. PMID: 25542836. DOI: 10.1093/molehr/gau114

74 Dietrich CU, Pandis N, Andersen JA and Heim S: Chromosome abnormalities in adenolipomas of the breast: karyotypic evidence that the mesenchymal component constitutes the neoplastic parenchyma. Cancer Genet Cytogenet *72(2)*: 146-150, 1994. PMID: 8143274. DOI: 10.1016/0165-4608(94)90131-7

75 Rohen C, Caselitz J, Stern C, Wanschura S, Schoenmakers EF, Van de Ven WJ, Bartnitzke S and Bullerdiek J: A hamartoma of the breast with an aberration of 12q mapped to the MAR region by fluorescence *in situ* hybridization. Cancer Genet Cytogenet *84(1)*: 82-84, 1995. PMID: 7497449. DOI: 10.1016/0165-4608(95)00060-7

76 Dal Cin P, Wanschura S, Christiaens MR, Van den Berghe I, Moerman P, Polito P, Kazmierczak B, Bullerdiek J and Van den Berghe H: Hamartoma of the breast with involvement of 6p21 and rearrangement of HMGIY. Genes Chromosomes Cancer *20(1)*: 90-92, 1997. PMID: 9290959. DOI: 10.1002/(sici)1098-2264(199709)20:1<90::aid-gcc13>3.0.co;2-j

77 Fletcher JA, Pinkus GS, Weidner N and Morton CC: Lineage-restricted clonality in biphasic solid tumors. Am J Pathol *138(5)*: 1199-1207, 1991. PMID: 1708947.

78 Fletcher JA, Pinkus GS, Donovan K, Naeem R, Sugarbaker DJ, Mentzer S, Pinkus JL and Longtine J: Clonal rearrangement of chromosome band 6p21 in the mesenchymal component of pulmonary chondroid hamartoma. Cancer Res *52(22)*: 6224-6228, 1992. PMID: 1423265.

79 Fletcher JA, Pinkus JL, Lage JM, Morton CC and Pinkus GS: Clonal 6p21 rearrangement is restricted to the mesenchymal component of an endometrial polyp. Genes Chromosomes Cancer *5(3)*: 260-263, 1992. PMID: 1384681. DOI: 10.1002/gcc.2870050315

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