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# Fusion of High Mobility Group AT-hook 2 Gene (*HMGA2*) With the Chromosome 12 Open Reading Frame 42 Gene (*C12orf42*) in an Aggressive Angiomyxoma With del(12)(q14q23) as the Sole Cytogenetic Anomaly

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**Abstract.** *Background/Aim: Aggressive angiomyxomas are mostly found in the pelvic and perineal region and are prone to recur after surgery. Cytogenetic information is available on only nine such tumors. Herein, we report the cytogenetic anomaly and its molecular consequence in another aggressive angiomyxoma. Materials and Methods: An aggressive angiomyxoma found in a 33-year-old woman was examined using cytogenetic, RNA sequencing, reverse transcription polymerase chain reaction (RT-PCR), and Sanger sequencing techniques. Results: The karyotype of short-term cultured tumor cells was 46,XX,del(12)(q14q23)[9]/46,XX[2]. RNA sequencing detected fusion of the high mobility group AT-hook 2 gene (HMGA2) with the chromosome 12 open reading frame 42 gene (C12orf42). RT-PCR together with Sanger sequencing verified the presence of an HMGA2::C12orf42 fusion transcript. Conclusion: The present case carrying del(12)(q14q23) and an HMGA2::C12orf42 chimeric transcript strengthens the notion that involvement of HMGA2 and its misexpression are pathogenetically important in the development of aggressive angiomyxomas.*

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*Key Words:* Aggressive angiomyxoma, chromosomal aberration, interstitial deletion del(12)(q14q23), high mobility group AT-hook 2 (*HMGA2*) gene, chromosome 12 open reading frame 42 (*C12orf42*) gene, *HMGA2::C12orf42* fusion transcript.



Aggressive angiomyxoma was first described by Steeper and Rosai as a distinctive, infiltrating soft-tissue tumor of the pelvis and perineum in nine female patients (1). The authors used the term "aggressive angiomyxoma" to emphasize the infiltrative nature of the neoplastic blood vessels and the fact that the tumor often recurs after surgery (1). Although aggressive angiomyxoma most often arises in the vulvovaginal region, perineum, and pelvis of reproductive age women (1-9), it has also been described in the scrotum, spermatic cord, and perineum of men (10-14). The larynx, oral floor, lung, supraclavicular fossa, and liver have also very occasionally been the sites of aggressive angiomyxomas (15-21). The tumors are composed of spindle cells that are immunohistochemically positive for desmin and vimentin. Numerous thick-walled blood vessels are embedded in an abundant myxoid matrix (9, 22). Over the years, cytogenetic information has been reported on only nine such tumors, all of them of vulvovaginal origin (Table I) (2, 3, 5-7, 23-27).

Herein, we report an aggressive angiomyxoma carrying a del(12)(q14q23) as the sole cytogenetic anomaly, resulting in fusion of the high mobility group AT-hook 2 (*HMGA2*) gene from 12q14 with the chromosome 12 open reading frame 42 (*C12orf42*) gene from 12q23.

## 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 perineum of a 33-year-old woman. Microscopically, the tumor had characteristic spindled to stellate cells scattered in a myxoid and

Table I. *Genetically examined aggressive angiomyxomas, published and present case.*

| Sex/Age (Years) | Location | Reported abnormal karyotype | *HMGA2* status | Reference |
|---|---|---|---|---|
| F/42 | Ischiorectal fossa | 45-50,XX,-12,-5,+der(5)t(5q15;?),-16,+der(16)t(5q;16q),-15,+der(15)t(15q13;?)(1-4),+/-frag | Not examined | Horsman *et al*. 1991 (23) |
| F/32 | Vaginal wall | 46,XX,t(7;12)(q22-31;q13-14) | Not examined | Betz *et al*. 1995 (24) |
| F/44 | Not available | 46,XX,der(5)t(5;12)(q31;p11),der(12)t(5;12)(q31;p11)inv(12)(p11q14) | Fusion with sequence from 12p11 | Kazmierczak *et al*. 1995, 1998 (25, 27) |
| F/16 | Vagina | 45,X,-X | Not examined | Kenny-Moynihan *et al*. 1996 (26) |
| F/24 | Vagina | 46,XX,t(8;12)(p12;q15) | Expression | Nucci *et al*. 2001 (2) |
| F/44 | Right labium majus | 46,XX,t(11;12)(q23;q15) | Expression | Micci *et al*. 2006 (3) |
| F/45 | Right side of the rectovaginal septum | 46,XX,t(5;8)(p15;q22) | Not examined | Tsuji *et al*. 2007 (6) |
| F/53 | Vagina | 46,XX,t(1;12)(p32;q15) | Fusion with sequence from 1p32.2 | Medeiros *et al*. 2007 (5) |
| F/72 | Rectal wall | 46,XX,t(12;21)(q15;q21) | Rearrangement | Rawlinson *et al*. 2008 (7) |
| F/44 | Vulva | Not done | *HMGA2::YAP1* | Lee M-Y *et al*. 2019 (34) |
| F/33 | Perineum | 46,XX,del(12)(q14q23) | *HMGA2::C12orf42* | Panagopoulos *et al*. 2022 (present case) |

collagenous matrix with differently sized vessels spread throughout the lesion (Figure 1A). There was no atypia or necrosis. The scattered cells showed strong cytoplasmic immunohistochemical positivity for desmin (Figure 1B). Smooth muscle actin (SMA) positivity was seen in nodules close to some of the vessels (Figure 1C). Nuclear positivity for estrogen receptor (ER) and progesterone receptor (PGR) was seen in all cells (Figure 1D and E). The diagnosis was aggressive angiomyxoma.

*G-banding and karyotyping*. Part of the resected tumor was received for cytogenetic analysis according to our diagnostic routine. The tumor specimen was minced with scalpels into 1-2 mm fragments and then enzymatically disaggregated with collagenase II (Worthington, Freehold, NJ, USA). The resulting cells were cultured, harvested, and processed for cytogenetic examination using standard techniques (28). Chromosome preparations were G-banded with Wright's stain (Sigma-Aldrich, St Louis, MO, USA) and examined (28). 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 (29).

*RNA sequencing*. Total RNA was extracted from a frozen (–80˚C) part of the tumor specimen, adjacent to that used for cytogenetic analysis and histologic examination, using miRNeasy Mini Kit (Qiagen, Hilden, Germany). One μg 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 $185\times10^6$ 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 FusionCatcher was used for the detection of possible *HMGA2* fusion transcripts (30, 31).

*Reverse transcription (RT) PCR and Sanger sequencing analyses*. In order to confirm the existence of *HMGA2* fusion (see below), RT-PCR and Sanger sequencing analyses were performed. cDNA was synthesized from one 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 of 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 Version (Takara Bio Europe/SAS, Saint-Germain-en-Laye, France) and 0.4 μM of each of the forward and reverse primers (Table II). The primer combination ABL1-91F1/ABL1-404R1 was used to amplify a 338 bp cDNA fragment from the *ABL1* gene (ABL proto-oncogene 1, non-receptor tyrosine kinase) in order to check the quality of the cDNA synthesis. To detect the *HMGA2::C12orf42* fusion transcript, the primer combinations HMGA2-929F1/C12orf42-1144R1 and HMGA2-929F1/C12orf42-1093R1 were used.

A C-1000 Thermal cycler (Bio-Rad) was used for PCR amplifications. 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 μl 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 the MinElute PCR Purification Kit (Qiagen) and Sanger sequenced with the dideoxy procedure using the BigDye Direct Cycle Sequencing Kit in accordance with the company's recommendations (ThermoFisher Scientific, Waltham, MA, USA). The primers used for sequencing were the forward HMGA2-929F1 containing M13 forward sequence at its 5´-end (M13-forward-HMGA2-929F1: TGTAAAACGACGGCCAGT-ACCGGTGAGCCC TCTCCTAAGAG) and the reverse C12orf42-1093R1 containing the M13 reverse primer sequence at its 5´-end (M13-reverse- C12orf42-1093R1: CAGGAAACAGCTATGACC-TTCCCTAGAGCTGTTGCA AAGTTGTT). Sequencing was run on the Applied Biosystems SeqStudio Genetic Analyzer system (ThermoFisher Scientific).

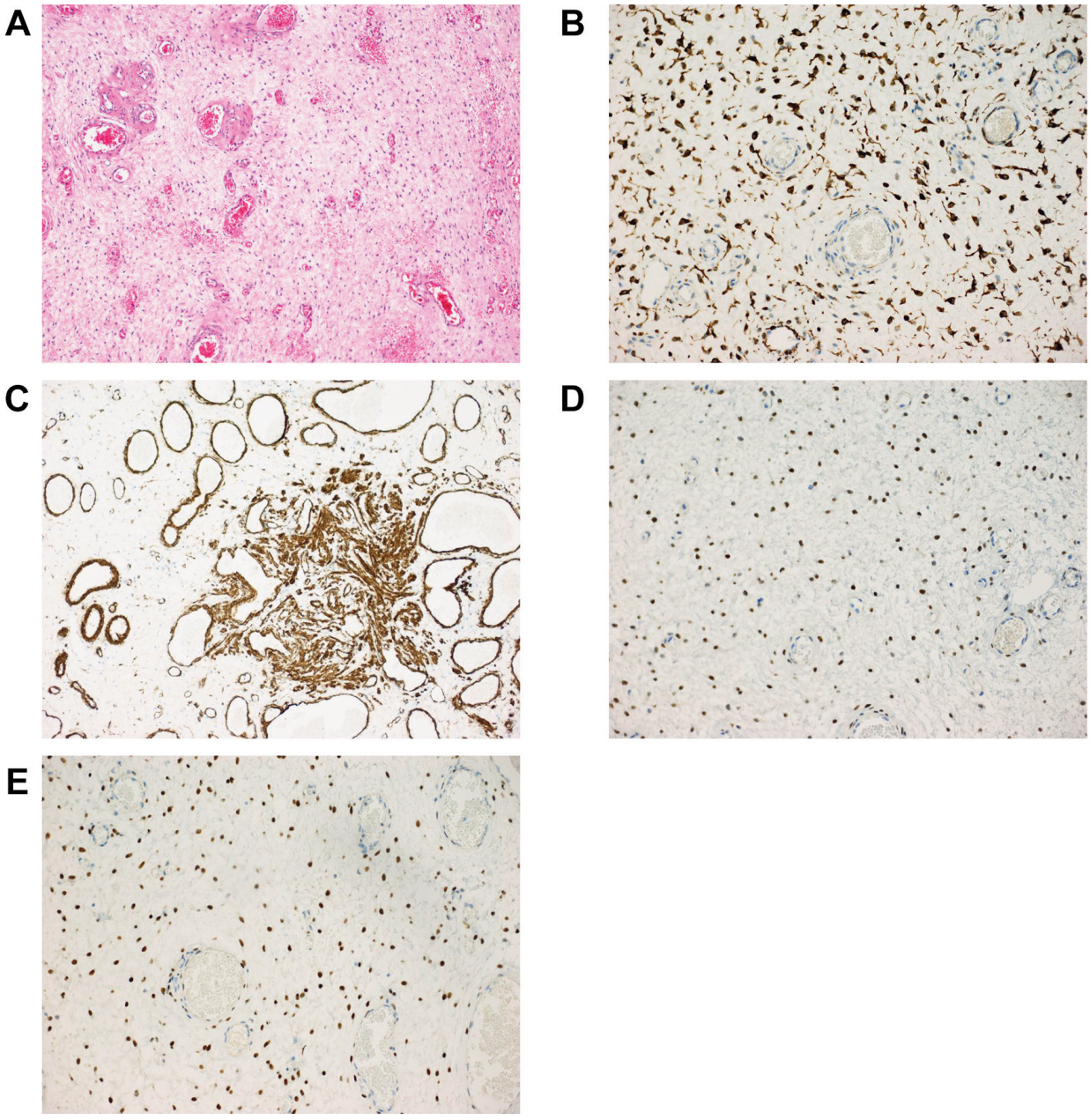


Figure 1. *Microscopic examination of the aggressive angiomyxoma. (A) Hematoxylin and eosin (HE)-stained section showing characteristic spindled to stellate cells scattered in a myxoid and collagenous matrix as well as differently sized vessels throughout the lesion, ×10. (B) Scattered cells showing strong cytoplasmic staining with desmin, ×10. (C) SMA positivity was seen in nodules close to some of the vessels, ×10. (D) Estrogen receptor (ER) nuclear positivity in all cells, ×10. (E) Progesterone receptor (PR) nuclear positivity in all cells, ×10.*

The Basic Local Alignment Search Tool (BLAST) was used to compare the sequences obtained by Sanger sequencing with the NCBI reference sequences NM_003483.4 of *HMGA2* and NM_001386867.1 (transcript variant 6) and NR_170336.1 (transcript variant 15, non-coding RNA) of *C12orf42* (32). The BLAST-like alignment tool (BLAT) and the human genome browser at UCSC were used to map the sequences on the Human GRCh37/hg19 assembly (33).

## Results

The G-banding analysis detected an interstitial deletion, del(12)(q14q23), as the sole karyotypic aberration in 9 of 11 examined metaphases. Thus, the karyotype was 46,XX,del(12)(q14q23)[9]/46,XX[2] (Figure 2A).

Table II. *Primers used for reverse transcription (RT)PCR amplification.*

| Designation | Sequence (5´->3´) | Position | Reference sequence | Gene (symbol) |
|---|---|---|---|---|
| ABL1-91F1 | CAG CGG CCA GTA GCA TCT GAC TTT G | 91-115 | NM_005157.4 | ABL proto-oncogene 1, non-receptor tyrosine kinase (*ABL1*) |
| ABL1-404R1 | CTC AGC AGA TAC TCA GCG GCA TTG C | 428-404 | NM_005157.4 | ABL proto-oncogene 1, non-receptor tyrosine kinase (*ABL1*) |
| HMGA2-929F1 | ACC GGT GAG CCC TCT CCT AAG AG | 929-951 | NM_003483.4 | High mobility group AT-hook 2 (*HMGA2*) |
| C12orf42-1144R1 | CGA AAA TCG CTC TTG GAG TCT CCT | 1167-1144 | NM_001386867.1 | Chromosome 12 open reading frame 42 (*C12orf42*) |
| C12orf42-1093R1 | TTC CCT AGA GCT GTT GCA AAG TTG TT | 1118-1093 | NM_001386867.1 | Chromosome 12 open reading frame 42 (*C12orf42*) |

Analysis of the fastq files of the RNA sequencing data with the FusionCatcher software detected an *HMGA2::C12orf42* chimeric transcript in which exon 4 of *HMGA2* (nt 1093 in reference sequence with accession number NM_003483.4) was fused with the last, non-coding exon 7 of the *C12orf42* reference sequence with accession number NM_001386867.1, which is identical to exon 11 in the *C12orf42* reference sequence NR_170336.1 (transcript variant 15, non-coding RNA).

RT-PCR with the primer combinations HMGA2-929F1/C12orf42-1144R1 and HMGA2-929F1/C12orf42-1093R1, as well as further Sanger sequencing of the cDNA amplified fragments, verified the above-mentioned *HMGA2::C12orf42* chimeric transcript (Figure 2B and C). The transcript was predicted to code for a putative 106 amino acid long peptide containing amino acid residues 1-94 of HMGA2 protein (accession number NP_003474.1), corresponding to exons 1-4 of the gene, and 12 amino acid residues from the sequence from C12orf42 (ETTRRCICLNKK) (Figure 2D).

## Discussion

Genetic studies of aggressive angiomyxomas are very few but overwhelmingly implicate the *HMGA2* gene in tumorigenesis (2-5, 7, 25, 27, 34). Out of nine published tumors with cytogenetic information, six had rearrangements of chromosomal bands 12q13-15 (Table I) (2, 3, 5, 7, 24, 25, 27), one had monosomy 12 among other changes (23), the eighth tumor showed monosomy of the X chromosome as the sole karyotypic aberration (26), and the ninth carried a t(5;8)(p15;q22) as the sole chromosomal change (6). Structural rearrangements of chromosome bands 12q13-15 are often found in benign mesenchymal tumors including soft tissue chondromas, lipomas, pulmonary chondroid hamartomas, and uterine leiomyomas; their common molecular denominator is rearrangement and transcriptional activation of the *HMGA2* gene in 12q14 (35, 36).

In three studies, metaphase and/or interphase fluorescence in situ hybridization (FISH) experiments on aggressive angiomyxomas with break-apart probes for *HMGA2* were performed, showing abnormal hybridization patterns indicative of *HMGA2* rearrangement (4, 5, 7). In the large interphase FISH study by Madeiros and coworkers (5), 14 out of 42 tumors (33%) showed *HMGA2* rearrangement.

At the molecular level, Kazmierczak and coworkers (25) detected an *HMGA2*-fusion transcript in an aggressive angiomyxoma with the karyotype 46,XX,der(5)t(5;12)(q31;p11), der(12)inv(12)(p11q15)t(5;12)(q31;p11) (it is often impossible to distinguish bands 12q14 and 12q15 in G-banded preparations). The chimeric transcript contained the first three exons of *HMGA2* followed by an intergenic sequence from 12p11. This would correspond to a truncated peptide containing the first 83 amino acid residues of *HMGA2*, encoding the AT-hook domains (exons 1-3 of *HMGA2*) that bind to the minor groove of adenine-thymine (AT) rich DNA, and 7 amino acid residues (NKQDSQE) from the BF510360 sequence (27).

In an aggressive angiomyxoma with t(1;12)(p32;q15), Madeiros and coworkers (5) found two chimeric transcripts in which exon 5 of *HMGA2*, 81 bp after the stop codon, was fused with sequences from chromosome sub-band 1p32.2 (GenBank accession numbers EU004592 and EU004592).

Recently, Lee and coworkers (34) reported a chimeric *HMGA2* transcript in which the first three exons of *HMGA2* were fused in frame with exons 2 to 7 of the Yes1 associated transcriptional regulator gene (*YAP1*) from 11q22, in an aggressive angiomyxoma. The putative HMGA2::YAP1 protein would contain, in addition to the three AT-hook domains of HMGA2, all functional domains of YAP1 except its proline N-terminal part which is encoded by exon 1 of that gene.

The aggressive angiomyxoma we describe had an interstitial deletion, del(12)(q14q23), as the sole karyotypic aberration. It resulted in an *HMGA2::C12orf42* chimeric transcript in which exon 4 of *HMGA2* was fused with the last, non-coding exon 7 of *C12orf42*. The transcription of *HMGA2* is from centromere to telomere whereas the transcription of *C12orf42* is from telomere to centromere. Thus, additional submicroscopic genomic rearrangements, perhaps an inversion, probably accompanied the interstitial del(12)

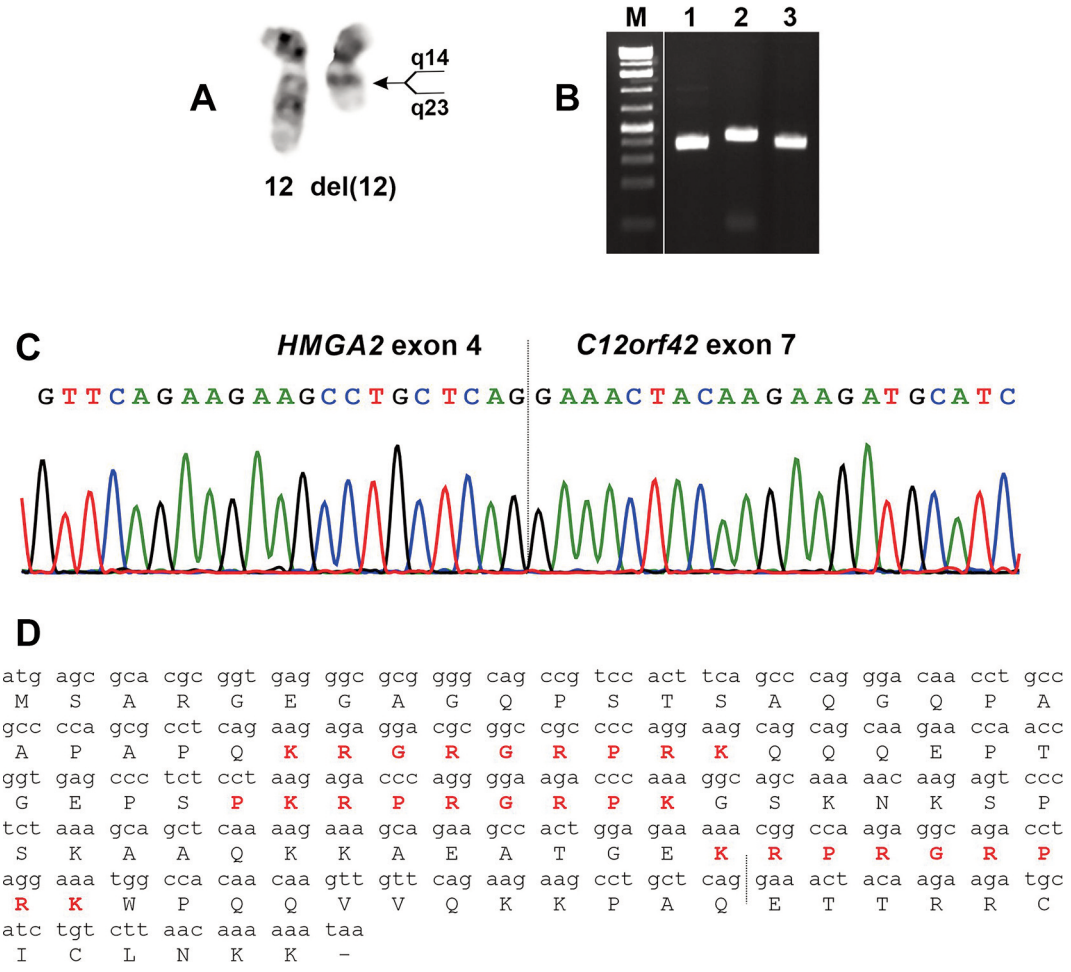


Figure 2. *Genetic analyses of the aggressive angiomyxoma. (A) Partial karyotype showing del(12)(q14q23) together with the normal chromosome 12. Arrow indicates breakpoints. (B) Gel electrophoresis of reverse transcription (RT) PCR amplification products: Lane 1, amplification of a 338 bp ABL1 cDNA fragment using the primers ABL1-91F1 and ABL1-404R1; lane 2, amplification of an HMGA2::C12orf42 cDNA fragment with the primers HMGA2-929F1/C12orf42-1144R1; lane 3, amplification of an HMGA2::C12orf42 cDNA fragment with the primers HMGA2-929F1/C12orf42-1093R1. (C) Partial sequence chromatogram of the cDNA HMGA2::C12orf42 fragment amplified with the primers HMGA2-929F1/C12orf42-1144R1 showing the junction position of HMGA2 and C12orf42 (vertical dotted line). Exon 3 of HMGA2 is based on reference sequence NM_003483.4 corresponding to transcript variant 1of HMGA2. Exon 7 of C12orf42 is based on reference sequence NM_001386867.1 corresponding to transcript variant 6 of C12orf42. (D) The putative 106 amino acid long HMGA2 peptide containing amino acid residues 1-94 of HMGA2 (accession number NP_003474.1) corresponding to exons 1-4 of the gene, and 12 amino acid residues from the sequence from C12orf42 (ETTRRCICLNKK). The three AT-hook domains of HMGA2 are shown with red bold letters.*

enabling the generation of a *HMGA2::C12orf42* chimera. Regardless, the *HMGA2::C12orf42* transcript would code for a peptide containing amino acid residues 1-94 of HMGA2 protein (the AT-hook domains) and 12 amino acid residues from the sequence from *C12orf42* (ETTRRCICLNKK) (Figure 2D).

In two other aggressive angiomyxomas, which carried chromosome translocations t(8;12)(p12;q15) and t(11;12)(q23;q15) as sole anomalies, FISH and molecular investigations showed that the breakpoints on chromosome 12 were outside *HMGA2* so that the entire coding part of *HMGA2* was expressed (2, 3). In the aggressive angiomyxoma with t(8;12)(p12;q15), FISH analysis placed the breakpoint telomeric to *HMGA2*. Immunohistochemistry showed that the HMGA2 protein was localized in spindle-shaped tumor cells (2). In another three studies in which *HMGA2* expression of aggressive angiomyxomas was assessed by immunohistochemical techniques, the HMGA2 protein was found in 90% of the tumors in two studies (37, 38) but in 68% in the third one (39).

The data presented above demonstrate a variability in transcriptional activation of *HMGA2* (breakpoints within or

outside *HMGA2*, different fusion partners, truncated or full-length HMGA2 protein or chimeric HMGA2-YAP1 protein) (2, 3, 5, 7, 27, 34). This variability is comparable to what is found in other benign mesenchymal tumors showing involvement of *HMGA2*, among them lipomas, pulmonary chondroid hamartomas, soft tissue chondromas, and uterine leiomyomas (36, 40-48).

Disruption of the *HMGA2* locus thus separates exons 1-3 that code for the three AT-hook domains, from the 3´-untranslated region of the gene (3´-UTR) which regulates *HMGA2* transcription (49-53). The existence of translocation breakpoints outside of the *HMGA2* locus (upstream or downstream) suggests that dysregulation of *HMGA2* by a mechanism different from that targeting the gene's 3´-UTR (2, 3, 43, 47, 48, 54, 55) may also be important.

It is important to note that evidence for the involvement of truncated forms of *HMGA2* and abnormal expression of full length *HMGA2* in tumorigenesis also stems from studies of cultured cells and murine models (56-62). Thus, expression of truncated human *HMGA2* encoding the three AT hook domains or *HMGA2-LPP* fusion transcript coding for the three AT hook domains of HMGA2 and the LIM domains of the lipoma preferred partner gene (LPP) protein resulted in neoplastic transformation of mouse embryonic fibroblasts (NIH3T3 cells) (56). Expression of truncated human *HMGA2* caused otherwise normal human myometrial cells to form leiomyoma-like lesions (62). In an *in vitro* system using porcine chondrocytes from the elbow joint, recombinant HMGA2 protein significantly increased the proliferative activity of chondrocytes in a dose-dependent manner. Application of a truncated HMGA2 peptide containing the first two AT-hook domains of HMGA2 showed a growth-promoting effect similar to that of the wild type HMGA2 protein (60, 61). In transgenic mice, expression of truncated *HMGA2* or overexpression of full-length protein gave rise to lipomas (57), mixed growth hormone/prolactin cell pituitary adenomas (58) or other neoplasms such as fibroadenomas of the breast and salivary gland adenomas (59). Finally, *HMGA2* was in knockout mice found to be a key regulator of myoblast proliferation and myogenesis (63). Hmga2 knockout mice had reduced myoblast proliferation and less muscle growth whereas overexpression of the gene promoted myoblast growth (63).

In summary, the present case with del(12)(q14q23) as the sole karyotypic change demonstrated generation of an *HMGA2::C12orf42* chimeric transcript as the key pathogenetic event. It underscores the notion that involvement of *HMGA2* and/or its misexpression is central to the development of aggressive angiomyxoma.

## Conflicts of Interest

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

## Authors' Contributions

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

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