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Fusion of the High-mobility Group AT-Hook 2 (*HMGA2*) and the Gelsolin (*GSN*) Genes in Lipomas With t(9;12)(q33;q14) Chromosomal Translocation

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Abstract. *Background/Aim: Lipomas are benign tumors composed of mature fat cells. They are common soft tissue tumors that often carry chromosome aberrations involving 12q14 resulting in rearrangements, deregulation, and generation of chimeras of the high-mobility group AT-hook 2 gene (HMGA2) which maps in 12q14.3. In the present study, we report the finding of t(9;12)(q33;q14) translocation in lipomas and describe its molecular consequences. Materials and Methods: Four lipomas from two male and two female adult patients were selected because their neoplastic cells carried a t(9;12)(q33;q14) as the sole karyotypic aberration. The tumors were investigated using RNA sequencing, reverse transcription polymerase chain reaction (RT-PCR), and Sanger sequencing techniques. Results: RNA sequencing of a t(9;12)(q33;q14)-lipoma detected an in-frame fusion of HMGA2 with the gelsolin gene (GSN) from 9q33. RT-PCR together with Sanger sequencing confirmed the presence of an HMGA2::GSN chimera in the tumor as well as in two other tumors from which RNA was available. The chimera was predicted to code for an HMGA2::GSN protein which would contain the three AT-hook domains of HMGA2 and the entire functional part of GSN. Conclusion: t(9;12)(q33;q14) is a recurrent cytogenetic aberration in lipomas and generates an HMGA2::GSN chimera. Similar to what is seen in other rearrangements of HMGA2 in mesenchymal tumors, the translocation physically separates the part of HMGA2 encoding AT-hook domains from the gene's 3´-terminal part which contains elements that normally regulate HMGA2 expression.*

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Key Words: Lipoma, chromosomal translocation, t(9;12)(q33;q14), high mobility group AT-hook 2 (*HMGA2*) gene, gelsolin gene (*GSN*), *HMGA2::GSN* chimera.

Lipomas are benign tumors composed of mature fat cells (1, 2). They are common in adults where they may occur both subcutaneously and as deep-seated lesions. Most lipomas are easily diagnosed as such, but those occurring deep down (intramuscular lipoma and perineural lipoma) may be confused with liposarcomas (1, 2).

Cytogenetic examinations of lipomas have shown that they often carry chromosome aberrations involving 12q14 (3-9). These aberrations result in rearrangements involving truncation, deregulation, and generation of chimeras of the high-mobility group AT-hook 2 gene (*HMGA2*) which is found in chromosome subband 12q14.3 (10-17). The recombination of 12q14 involves a wide variety of partners (8, 9, 16-18). The by-far most common event is the translocation t(3;12)(q28;q14) which fuses *HMGA2* with a gene from 3q28 named LIM domain containing preferred translocation partner in lipoma (*LPP*) (3-11, 19), but also many other genomic recombinations giving rise to *HMGA2* chimeric genes have been reported in lipomas (Table I) (10-15, 19-27). In the present study, we describe the specific translocation t(9;12)(q33;q14) and its molecular consequences in four lipomas.

Materials and Methods

Patients. Table II shows the patient sex, age, diagnosis, and tumor location and size. All tumors were surgically removed. The study

Table I. *Genomic aberrations in lipomas giving rise to the high-mobility group AT-hook 2 (HMGA2) gene (on 12q14) truncation or in-frame fusions (denoted with *).*

Aberration	Partner gene full name (gene symbol)	References
t(1;12)(p32;q14)	Phospholipid phosphatase 3 (*PLPP3*)	(20)
t(2;12)(q37;q14)	Atypical chemokine receptor 3 (*ACKR3*)	(12, 21)
t(3;12)(q28;q14)	LIM domain containing preferred translocation partner in lipoma (*LPP*)	(10, 11, 19, 22)
t(4;12)(q27~28;q14~15)	Intergenic region of 4q28.1	(15)
t(5;12)(q33;q14)	EBF transcription factor 1 (*EBF1*)	(13)
t(9;12)(p22;q14)	Nuclear factor I B (*NFIB*)	(23-26)
t(12;13)(q14;q13)	LHFPL tetraspan subfamily member 6 (*LHFPL6*)	(27)
t(12;18)(q14~q15;q12~q14)	Glutamate receptor interacting protein 1 (*GRIP1*)	(14)
t(12;18)(q14;q12)	SET binding protein 1 (*SETBP1*)	(14)
t(12;18)(q14;q12)	Intergenic region of 18q12.3	(14)

Table II. *Clinical, cytogenetic, and molecular data on the four lipomas.*

Lipoma	Sex/Age	Region	Size (cm)	Karyotype	Fusion gene
1	M/64	Gluteal region	12x9.5x4	46,XY,t(9;12)(q33;q14)[11]/46,XY[2]	N.A*
2	M/47	Thigh	4.5x4.2x1.5	46,XY,t(9;12)(q33;q14)[10]/46,XY[5]	*HMGA2::GSN*
3	F/68	Shoulder	7x6x4	46,XX,t(9;12)(q33;q14)[8]/46,XX[5]	*HMGA2::GSN*
4	F/56	Neck	10.5x9.5x2.8	46,XX,t(9;12)(q33;q14)[10]/46,XX[2]	*HMGA2::GSN*

N.A: Not available material.

Table III. *Designation, sequence (5´->3´), and position in reference sequences of the forward (F) and reverse (R) primers of the high mobility-group AT-hook 2 (HMGA2) and the gelsolin (GSN) genes, used for polymerase chain reaction (PCR) amplification and Sanger sequencing analyses.*

Designation	Sequence (5´->3´)	Reference sequence: Position
HMGA2-845F1	TCC ACT TCA GCC CAG GGA CAA	NM_003483.4: 845-865
HMGA2-929F1	ACC GGT GAG CCC TCT CCT AAG AG	NM_003483.4: 929-951
GSN-337R1	TAC TGC AGA TTT CCG TTC CTC AGC	NM_000177.5: 360-337
GSN-272R1	TCT CCA TAA AGG TTG GTG GGC AC	NM_000177.5: 294-272

was approved by the Regional Ethics Committee (Regional komité for medisinsk forskningsetikk Sør-Øst, Norge). All patient information has been de-identified.

Methods. All methods used in the present study have been described in many of our previous publications (14, 28-35). In brief, for cytogenetic analysis, samples from the surgical specimens were disaggregated and the resulting cells were cultured, harvested, and processed for cytogenetic examination using standard techniques (36, 37). Chromosome preparations were G-banded with Wright's stain (Sigma-Aldrich, St Louis, MO, USA) and examined. Metaphases were analyzed and karyograms prepared using the CytoVision computer-assisted karyotyping system (Leica Biosystems, Newcastle upon Tyne, UK). The karyotypes were designated according to the International System for Human Cytogenomic Nomenclature (38). For RNA sequencing and molecular analyses, total RNA from three of the lipomas was isolated from tissue adjacent to that used for cytogenetic analysis and histologic examination using miRNeasy kit, TissueLyser II homogenizer, and Qiacube according to the manufacturer's recommendations (Qiagen, Hilden, Germany). The RNA quality was evaluated with a 2100 Bioanalyzer system and RNA 6000 Nano Kit (Agilent, Santa Clara, CA, USA). One microgram of total RNA from tumor 4 (Table II) was sent to the Genomics Core Facility at the Norwegian Radium Hospital, Oslo University Hospital, for high-throughput paired-end RNA sequencing. Fusion transcripts were found using the FusionCatcher software (39, 40). For cDNA synthesis, 400-500 ng of total RNA were reverse-transcribed using iScript Advanced cDNA Synthesis Kit for RT-qPCR according to the manufacturer's instructions (Bio-Rad Laboratories, Hercules, CA, USA). cDNA equivalent to 20 ng/μl of total RNA was used as template in subsequent PCR assays. Outer PCRs were performed using the forward primer HMGA2-845F1 and the reverse primer GSN-337R1 (Table III). Nested (inner) PCRs were performed using the forward primer HMGA2-929F1 and reverse primer GSN-272R1 (Table III). Three μl of the PCR products were stained with GelRed (Biotium, Hayward, CA, USA), analyzed by electrophoresis through 1.0% agarose gel, and photographed. The remaining PCR products

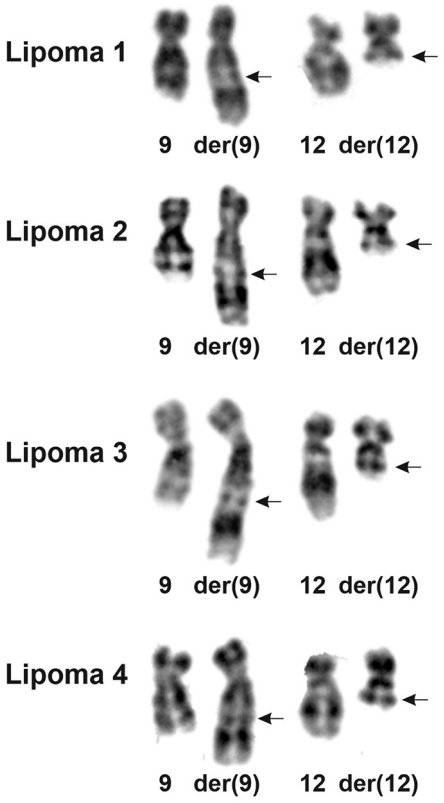

Figure 1. *G-banding analysis of lipomas. Partial karyograms showing the der(9)t(9;12)(q33;q14) and der(12)t(9;12)(q33;q14) together with the corresponding normal chromosome homologs; breakpoint positions are indicated by arrows.*

were purified with the MinElute PCR Purification Kit (Qiagen) and sequenced using Sanger sequencing methodology on the Applied Biosystems SeqStudio Genetic Analyzer system (ThermoFisher Scientific, Waltham, MA, USA). The Basic Local Alignment Search Tool (BLAST) was used to compare sequences obtained by Sanger sequencing with the NCBI reference sequences NM_003483.4 (*HMGA2*) and NM_000177.5 (*GSN*) (41).

Results

All four lipomas had the balanced translocation t(9;12)(q33;q14) as the sole karyotypic aberration (Figure 1, Table II); indeed, the tumors were selected for further studies because their neoplastic cells carried a t(9;12)(q33;q14) chromosome translocation.

Analysis using FusionCatcher of RNA sequencing data in the fastq files obtained from tumor 4 detected an *HMGA2::GSN* chimeric transcript in which exon 3 of *HMGA2* was fused in frame with exon 2 of *GSN* (fusion of nucleotide 1060 in reference sequence with accession number NM_003483.4 with nucleotide 176 in reference sequence NM_000177.5):

AGCCACTGGAGAAAAACGGCCAAGAGGCAGACC
TAGGAAATGG::CCCAACAGCATGGTGGTGGAACACC
CCGAGTTCCTCAAGGCAG.

Nested RT-PCR with the primer combinations HMGA2-845F1/GSN-337R1 and HMGA2-929F1/GSN-272R1, as well as further Sanger sequencing of the cDNA amplified fragments, verified the above-mentioned *HMGA2::GSN* chimeric transcript in tumor 4 (Figure 2A and B). The same analysis (nested RT-PCR/Sanger sequencing) detected an identical *HMGA2::GSN* chimeric transcript in tumors 2 and 3, the only other two tumors from which RNA was available (Table II).

Discussion

We showed that the chromosome translocation t(9;12)(q33;q14) is a recurrent cytogenetic aberration in lipomas leading to fusion of *HMGA2* with the *GSN* gene from 9q33. Because both genes are transcribed from centromere to telomere, the chimeric gene *HMGA2::GSN* is predicted to be generated on der(12)t(9;12)(q33;q14). The chromosome translocation t(9;12)(q33;q14) was previously reported in a deep-seated lipoma located in the thorax of a 72-year-old woman but that tumor was not subjected to molecular investigations (9). Recently, in an investigation of eleven lipoblastomas using targeted RNA sequencing methodology, the *HMGA2::GSN* chimera was found in a lipoblastoma located in the lower extremity of a 12-year-old boy (42). The fusion point in that case was identical to the *HMGA2::GSN* fusion points detected in the present study (42).

Gelsolin is an actin binding and calcium regulated protein which is involved in assembly and disassembly of actin filaments influencing cell morphology, differentiation, movement, and apoptosis (43-45). The *GSN* gene has many alternative splicing transcripts but in the main encodes two gelsolin isoforms: a 731 amino acid long/80 kDa cytosolic protein (NP_001121134.1) and a plasma 782 amino acid long/86 kDa in weight protein (NP_000168.1) found in the plasma of humans (46-48). Plasma gelsolin has a signal peptide not found in the cytosolic form of the protein (43-48). Depending on the type of neoplasm, gelsolin has been reported to have tumor suppression or oncogenetic function (44, 45).

Based on the reference sequences NM_003483.4/NP_003474.1 for *HMGA2* and NM_000177.5/NP_000168.1 for *GSN*, the *HMGA2::GSN* chimera is predicted to code for an 817 amino acid long peptide containing amino acid residues 1-83 from HMGA2 protein and 49-782 from GSN protein. Thus, HMGA2::GSN chimeric protein would contain the three AT-hook domains of HMGA2 and the entire functional part of GSN without the signal peptide which is found in the first 27 amino acids of native GSN protein (Figure 2B and C) (48, 49).

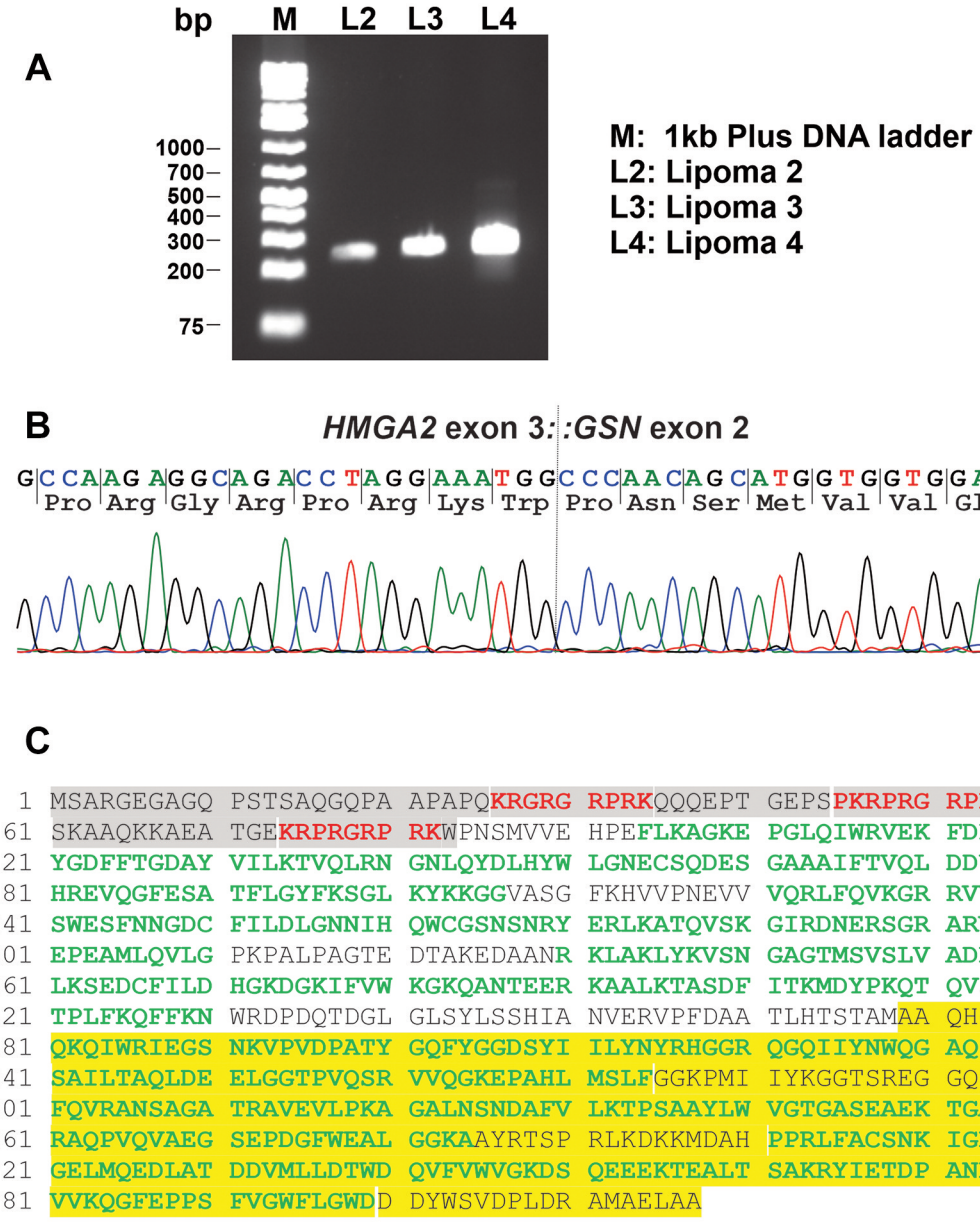

Figure 2. *Molecular genetic examination of lipomas. (A) Gel electrophoresis showing the amplified cDNA fragment using the primer combination HMGA2-929F1 and GSN-272R1. (B) Partial Sanger sequencing chromatogram of the amplified fragment showing the junction (vertical line) between exon 3 of HMGA2 and exon 2 of GSN. (C) The chimeric HMGA2::GSN protein. The HMGA2 part is in grey background. The AT-hook domains are shown with red bold letters. The actin-binding, calcium-sensitive area is in yellow background. The gelsolin like domains are shown with green bold letters.*

Very few *HMGA2* fusion genes result in chimeric HMGA2 proteins (17, 33). The *HMGA2::LPP* chimera found in lipomas, chondroid hamartomas, and chondromas codes for a chimeric HMGA2::LPP protein (10, 11, 19, 50-52). Fusion of *HMGA2* with the epidermal growth factor receptor gene (*EGFR*) from 7p11, reported in a single case of glioblastoma, generates a fusion gene coding for a chimeric HMGA2::EGFR protein (53). An in-frame fusion transcript of *HMGA2* with the Yes1-associated transcriptional regulator gene (*YAP1*) from 11q22 was reported in an aggressive angiomyxoma (54). Recently, fusion of *HMGA2* with the nuclear receptor co-repressor 2 gene (*NCOR2*) from 12q24.31 was described; the result is an HMGA2::NCOR2 chimeric protein found in osteoclastic giant cell-rich tumors of bone (31), giant cell-rich soft-tissue tumors expressing low- to high molecular weight keratins (55),

xanthogranulomatous epithelial tumor (56), and tenosynovial giant-cell tumor (57). Tumorigenic properties were detected for both the HMGA2::LPP (58-60) and HMGA2::EGFR fusion proteins (53), whereas functional studies have not been performed to test for the effects of HMGA2::YAP1, HMGA2::NCOR2, and the present HMGA2::GSN chimeric protein. Although the 3´-end partners (LPP, EGFR, YAP1, NCOR2, and GSN) in HMGA2 chimeric proteins are involved in different cell functions and have been implicated in tumor development (33), it is worthy of note that all the above-mentioned HMGA2-chimeras contain the three AT-hook domains of HMGA2 (17, 33). In this sense, the pattern is similar to what is seen in other rearrangements of *HMGA2* found in lipomas and other tumors, *i.e.*, disruption of the *HMGA2* locus leaves intact exons 1-3 of the gene which encode the AT-hook domains and separates them from the 3´-terminal part of the gene which contains regulatory elements for the expression of *HMGA2* (34, 61-63).

In conclusion, in the present study we showed that (9;12)(q33;q14) is a recurrent cytogenetic aberration in lipomas, and that the translocation generates an *HMGA2::GSN* fusion gene. The resulting fusion protein would contain the three AT-hook domains of HMGA2 and the entire functional part of GSN. In this manner, the part of HMGA2 encoding the AT-hook domains becomes physically separated from the 3´-terminal part of the gene which contains elements that regulate gene expression.

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. KA performed molecular genetic experiments and interpreted the data. MB performed molecular genetic experiments. LG performed cytogenetic analysis. ML-I performed 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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