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FOS-ANKH and *FOS-RUNX2* Fusion Genes in Osteoblastoma

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Abstract. *Background/Aim: Osteoblastoma is a rare benign tumor of the bones in which recurrent rearrangements of FOS have been found. Our aim was to investigate two osteoblastomas for possible genetic aberrations. Materials and Methods: Cytogenetic, RNA sequencing, and molecular analyses were performed. Results: A FOS-ANKH transcript was found in the first tumor, whereas a FOS-RUNX2 was detected in the second. Exon 4 of FOS fused with sequences either from intron 1 of ANKH or intron 5 of RUNX2. The fusion events introduced a stop codon and removed sequences involved in the regulation of FOS. Conclusion: Rearrangements and fusions of FOS show similarities with those of HMGA2 (a feature of leiomyomas and lipomas) and CSF1 (tenosynovial giant cell tumors). The replacement of a 3'-untranslated region, controlling the gene's expression, by a new sequence is thus a common pathogenetic theme shared by FOS, HMGA2, and CSF1 in many benign connective tissue tumors.*

Osteoblastoma is a rare benign tumor that accounts for 1% of all bone tumors. It is most often found in patients between 10 and 30 years of age and is 2.5 more common in males than females (1). The tumor was first described in 1956 in two different publications, one by Jaffe and the other by Lichtenstein (2, 3). In the 1970s, a more aggressive type of osteoblastoma was described under various names such as malignant osteoblastoma (4), aggressive osteoblastoma (5), and epithelioid osteoblastoma (6, 7). Recently, recurrent rearrangements of Fos proto-oncogene, AP-1 transcription factor subunit (*FOS*) and FosB proto-oncogene, AP-1 transcription factor subunit (*FOSB*) were described in osteoblastoma and the *FOS-ANKH, FOS-KIAA1199, FOS-MYO1B, FOS-IGR* (in two tumors), and *PPP1R10-FOSB* fusion genes were found in six tumors (8).

In a previous study using RNA sequencing and other molecular genetic techniques, we found fusion of the collagen type I alpha 1 (*COL1A1*) and the FYN proto-oncogene, Src family tyrosine kinase (*FYN*) genes in an epithelioid osteoblastoma (9). Herein, we used cytogenetic, RNA sequencing, and other molecular genetic techniques to find a novel fusion of *FOS* with RUNX family transcription factor 2 (*RUNX2* in chromosome band 6p21.1) in one tumor and fusion of *FOS* with ANKH inorganic pyrophosphate transport regulator (*ANKH* in chromosome band 5p15.2) in another osteoblastoma, proving that the *FOS-ANKH* fusion is recurrent in this tumor type.

Materials and Methods

Ethics statement. The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway (REK Sør-Øst; http://helseforskning.etikkom.no) and written informed consent was obtained from the patients' parents 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.

Case description

Case 1. The patient was a 7-year-old boy who had ongoing pain in his knee, worsening during the night. Curettage was performed.

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Case 2. The patient was an 11-year-old boy who has suffered from localized pain in his arm, worsening during the night and by frequent use. Clinically and radiologically the findings suggested osteoblastoma. The patient was operated on, with curettage, but histologically there was no tumor tissue. Radiofrequency ablation was tried 3 times, with only a short clinical effect. Open curettage was performed 2 years after first biopsy.

G-banding and karyotyping. Fresh tissue from a representative area of the tumors was short-term cultured and analyzed cytogenetically as previously described (10).

Fluorescence in situ hybridization (FISH). The BAC probes reported by Fitall *et al*. (8) were purchased from BACPAC Resource Center located at the Children's Hospital Oakland Research Institute (Oakland, CA) (https://bacpacresources.org/) (Table I). FISH analyses were performed on metaphases and interphase nuclei using a *FOS* (see below) home-made break-apart probe (Table I). Detailed information on the FISH procedure is given elsewhere (10).

RNA sequencing and reverse transcription (RT) PCR analyses. Total RNA was extracted from frozen (–80˚C) tumor tissue adjacent to that used for cytogenetic analysis and histologic examination using miRNeasy Mini Kit (Qiagen Nordic, Oslo, Norway) and 300 ng 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 deFuse software was used to find possible *FOS* fusion transcripts (11).

In order to confirm the existence of the *FOS-ANKH* and *FOS-RUNX2* fusion transcripts (see below), reverse transcription (RT) PCR and Sanger sequencing analyses were performed, as described previously (10). For the detection of *FOS-ANKH* fusion transcript, the primer combinations were the forward FOS-F1 together with the reverse ANKH-R1 and FOS-F2 together with the reverse ANKH-R2 (Table II). For the detection of *FOS-RUNX2* fusion transcript, the primer combinations were the forward FOS-F3 together with the reverse RUNX-R1 and FOS-F4 together with the reverse RUNX-R2 (Table II). Cycling was performed at 94˚C for 30 sec followed by 35 cycles of 7 sec at 98˚C, 30 sec at 60˚C, 30 sec at 72˚C, and a final extension for 5 min at 72˚C. The BLAST software (http://blast.ncbi.nlm.nih.gov/Blast.cgi) was used for computer analysis of sequence data.

Results

Case 1. The G-banding analysis of short-term cultured tumor cells revealed the karyotype 46,XY,der(13;14)(q10;q10)c[6]/46,Y,der(X)t(X;3)(p22;p14~21),der(3)t(3;14)(p14~21;q23~24),add(5)(p15),der(13;14)ct(X;14)(p22;q23~24),add(22)(q12~13)[9] (Figure 1A). No material was available to perform FISH analysis, nor did we have a blood sample for verification that the Robertsonian 13;14-translocation was indeed constitutional.

Using the deFuse software on the fastq files of the RNA sequencing data, a *FOS-ANKH* fusion transcript was found (Figure 1B).

RT-PCR with the primer combinations FOS-F1/ANKH-R1 and FOS-F2/ANKH-R2 amplified a 296 bp fragment and a 168 bp fragment, respectively (data not shown). Direct sequencing of the PCR fragments showed that they were *FOS-ANKH* chimeric cDNA fragments (Figure 1C). There was a two nucleotides discrepancy at the fusion point between Sanger sequencing and that found by analysis of the RNA sequencing data using deFuse (Figure 1C). However, the discrepancy would not affect the ensuing output which is a TAG stop codon 6 nucleotides after the fusion point (Figures 1B and 1C). Thus, in the *FOS-ANKH* chimeric transcript, exon 4 of *FOS* (nt 1061 in reference sequence with accession number NM_005252.3) was fused with a sequence from intron 1 of *ANKH*. The *FOS-ANKH* transcript codes for a putative protein which contains amino acid residues 1-285 of the FOS protein (accession number NP_005243.1) followed by two amino acid residues from the intronic sequence of *ANKH*.

Case 2. The karyotype was normal 46,XY in 25 examined metaphase plates (data not shown). In FISH experiments, however, the *FOS* probe was found to be split in both metaphase spreads examined and in 6 out of 100 interphase nuclei (Figure 2A and B). Using the deFuse software on the fastq files of the RNA sequencing data, a *FUS-RUNX2* fusion transcript was found (Figure 2C).

RT-PCR with the primer combinations FOS-F3/RUNX2-R1 and FOS-F4/RUNX2-R2 amplified a 509 bp fragment and a 321 bp fragment, respectively (data not shown). Direct sequencing of the PCR fragments showed that they were *FOS-RUNX2* chimeric cDNA fragments with a fusion point identical to that found by analysis of the RNA sequencing data using deFuse (Figure 2D). Thus, in the *FOS-RUNX2* chimeric transcript, exon 4 of *FOS* (nt 945 in reference sequence with accession number NM_005252.3) was fused with a sequence from intron 5 of *RUNX2*. The *FOS-RUNX2* transcript codes for a putative protein which contains amino acid residues 1-247 of the FOS protein (accession number NP_005243.1) and 10 amino acid residues (VQRSHTTNDC) from the intronic sequence of *RUNX2*.

Discussion

We identified *FOS-ANKH* and *FUS-RUNX2* fusion genes in two osteoblastomas. The *FOS-ANKH* was previously reported in another osteoblastoma (8) but, to the best of our knowledge, not in other tumors. Thus, our data showed that *FOS-ANKH* is a recurrent fusion gene in osteoblastomas. In both cases, the one described here and the previously reported one, part of exon 4 of *FOS* (nt 1061 and 982, respectively) was fused with a sequence from intron 1 of *ANKH*.

The *FOS-RUNX2* fusion gene is reported here for the first time. Again, part of exon 4 of *FOS* was fused with an intronic sequence from the partner gene, in this case *RUNX2*.

The *FOS* gene is a part of the FOS family of transcription factors which consists of 4 members: *FOS* (on chromosome

Table I. *BAC probes used for FISH experiments.*

BAC clones	Chromosome band	Targeted gene	Position on GRCh38/hg38 assembly	Labelling
RP11-484J14	14q24.3	Centromeric-FOS	chr14:75060453-75231755	Green
RP11-652M15	14q24.3	Centromeric-FOS	chr14:74841928-75034860	Green
RP11-905L16	14q24.3	Centromeric-FOS	chr14:74617042-74814819	Green
RP11-782G23	14q24.3	Telomeric-FOS	chr14:75344174-75519840	Red
RP11-714F24	14q24.3	Telomeric-FOS	chr14:75541885-75739308	Red
RP11-68E9	14q24.3	Telomeric-FOS	chr14:75778914-75940947	Red

Table II. *Primers used for PCR amplification and Sanger sequencing analyses.*

Name	Sequence (5'->3')	Position	Reference number	Chromosome band
FOS-F1	GTGGAACCTGTCAAGAGCATCAG	962-984	NM_005252.3	14q24.3
ANKH-R1	ATTCATGTTGTGCTCTCAGAATGG	14789425-14789448	NC_000005.10	5p15.2
FOS-F2	CTGAAGACCGAGCCCTTTGAT	995-1015	NM_005252.3	14q24.3
ANKH-R2	TTCAGTGTTTGGCTTGGTAACCT	14789520-14789542	NC_000005.10	5p15.2
FOS-F3	AGACCGAGATTGCCAACCTGCT	744-765	NM_005252.3	14q24.3
RUNX2-R1	AGCGGCTCAAAGGGCTAGAGG	45483160-45483180	NC_000006.12	6p21.1
FOS-F4	ACCTGCCTGCAAGATCCCTGAT	808-829	NM_005252.3	14q24.3
RUNX2-R2	GCAGCCTTTCCCAGCAAAGATT	45483284-45483305	NC_000006.12	6p21.1

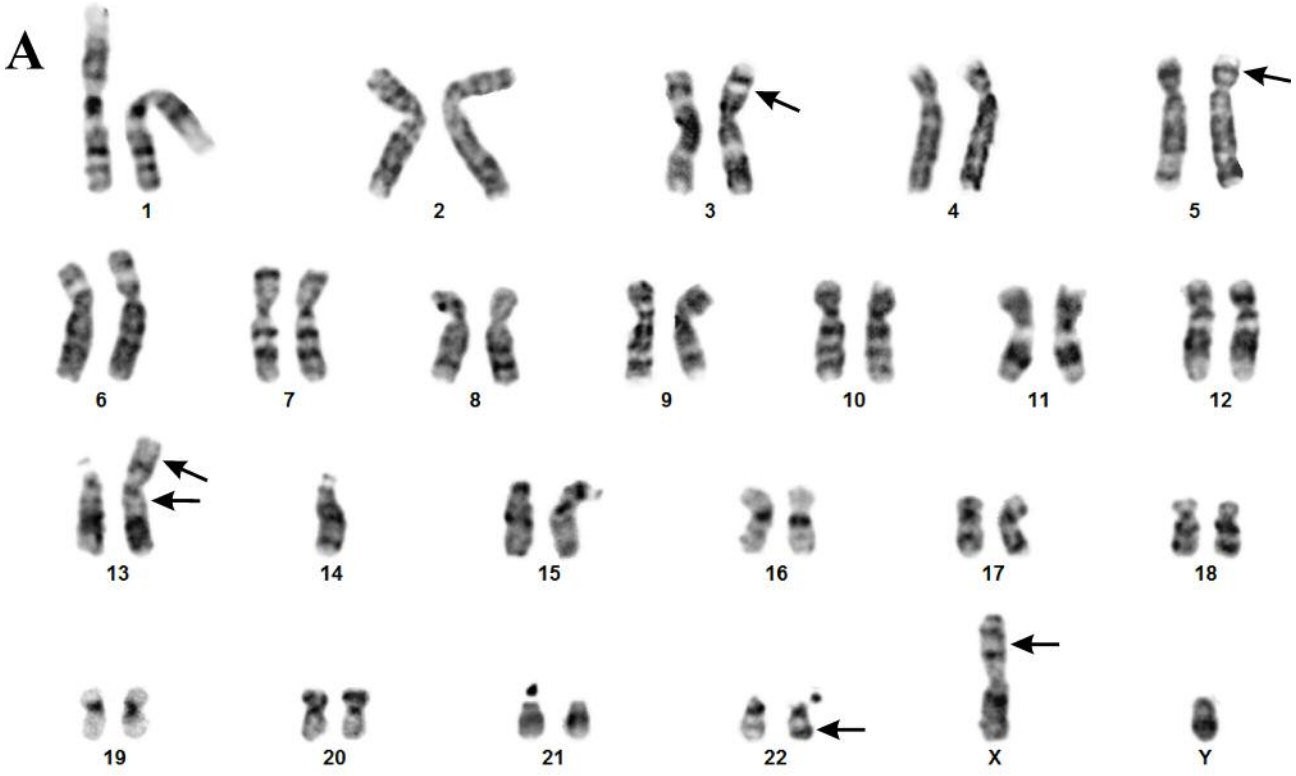
band 14q24.3), *FOSB* (on band 19q13.3), *FOSL1* (on band 11q13.1), and *FOSL2* (on band 2p23.2). These genes encode leucine zipper proteins that can dimerize with proteins of the JUN family, thereby forming the transcription factor complex AP-1 (12, 13). As such, the FOS proteins have been implicated as regulators of cell proliferation, differentiation, and transformation (12-16).

The amount of FOS protein in cells is tightly regulated at the transcriptional and translational levels and by interaction between transcription and translation (17-20). In the 3'-untranslated region (3'-UTR), there are two domains of AU-rich elements involved in the stability of *FOS* mRNA, a localization signal which binds the mRNA to the perinuclear cytoskeleton, a sequence that binds the miR-7b miRNA decreasing mRNA translation, and AU-rich regions which interact with parts of *FOS* coding regions facilitating mRNA deadenylation (poly(A) tail-shortening process) and decay by a mechanism coupled to translation (17, 19, 21-27). FOS is an unstable, easily degradable protein. The carboxy terminal part of FOS was found to be essential for FOS protein degradation (18, 20, 28-32).

Rearrangements and fusions of *FOS* have been reported in epithelioid hemangioma of the bone (*FOS-LMNA*, *FOS-MBNL1*, and *FOS-VIM*) as well as in osteoblastoma (*FOS-RUNX2*, *FOS-ANKH*, *FOS-CEMIP*, and *FOS-MYO1B*) (8, 33, 34). In all examined cases, the breakpoint occurred in exon 4 where the fusion event introduced a stop codon and removed both the C-terminal part of FOS, which is essential for FOS degradation, and the 3'- untranslated region of *FOS* mRNA which maintains *FOS* mRNA stability (8, 33, 34) .

The resulting, truncated FOS protein contains the N-terminal transactivation domain, which plays a crucial role in transformation, and the basic leucine zipper domain (bZIP) making it more stable than wild-type FOS (8, 20, 33-35). *In vitro* experiments have shown that truncated FOS protein is resistant to degradation and has a longer half-life than the wild-type FOS protein (*circa* 1-2 h) (20).

Rearrangements of *FOS* and its fusion with various partners share similarities with rearrangements and fusions of the *HMGA2* and *CSF1* genes. In lipomas and other benign connective tissue tumors, chromosome aberrations, mainly translocations, disrupt the *HMGA2* locus in 12q14 and fuse part of *HMGA2* with various partners (10, 36-42). In all reported cases, the pattern is the same: Disruption of the *HMGA2* locus leaves intact exons 1-3 which encode the AT-hook domains separating them from the 3'-untranslated region of the gene (3'-UTR). The 3'-UTR of HMGA2 was shown to regulate transcription of the *HMGA2* gene (43-45). Mouse embryonic NIH3T3 fibroblasts are transformed *in vitro* by the expression of truncated HMGA2 protein carrying the three DNA-binding domains (46). Overexpression of truncated HMGA2 in human myometrial cells was shown to induce leiomyoma-like lesions (47). Moreover, transgenic mice expressing a truncated form of the HMGA2 protein developed benign mesenchymal tumors (48, 49).



B

GAAAGGAATAAGATGGCTGCAGCCAAATGCCGCAACCGGAGGAGGGAGCTGACTGATACACT
CCAAGCGGAGACAGACCAACTAGAAGATGAGAAGTCTGCTTTGCAGACCGAGATTGCCAACC
TGCTGAAGGAGAAGGAAAAACTAGAGTTCATCCTGGCAGCTCACCGACCTGCCTGCAAGATC
CCTGATGACCTGGGCTTCCCAGAAGAGATGTCTGTGGCTTCCCTTGATCTGACTGGGGGCCT
GCCAGAGGTTGCCACCCCGGAGTCTGAGGAGGCCTTCACCCTGCCTCTCCTCAATGACCCTG
AGCCCAAGCCCTCAGTGGAACCTGTCAAGAGCATCAGCAGCATGGAGCTGAAGACCGAGCCC
TTTGATGACTTCCTGTTCCCAGCATCATCCAGGCCCAGTGGCTCTGAGACAG|AATTTTAGG
AGATTCCCTTTTATTCTCAATAAAATAGAAAGAAATATTTACTGTGGTTTATTCCTTAGTGT
TAAAGAGAGGTTACCAAGCCAAACACTGAATACTTTAGAAAATTTCTAGATAGACACAGCTT
AGAAATGGAGCTTAGCTTTTTTTTTTTTTTTTATCACCACCATTCTGAGAGCACAACATGAA
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GCATTTAACTCATACGGAAG

C

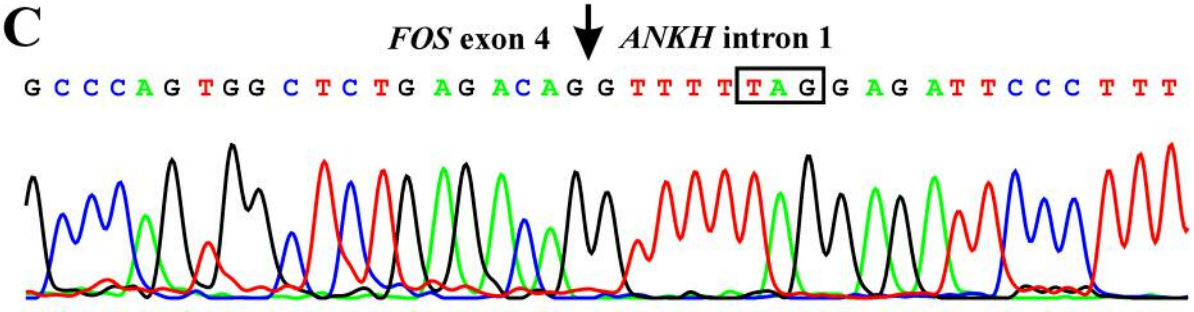

Figure 1. *Genetic analyses of the osteoblastoma of case 1. (A) Karyogram showing the chromosome aberrations (arrows). (B) FOS-ANKH fusion sequence obtained from the raw data using deFuse software after RNA sequencing. The G|A junction of FOS with ANKH is highlighted in red. The position of the forward FOS-F1 and reverse ANKH-R1 primers are highlighted in green. The position of the forward FOS-F2 and the reverse ANKH-R2 primers are highlighted in blue. (C) Partial sequence chromatogram of the cDNA amplified fragment showing the junction position of FOS with intron 1 of ANKH.*

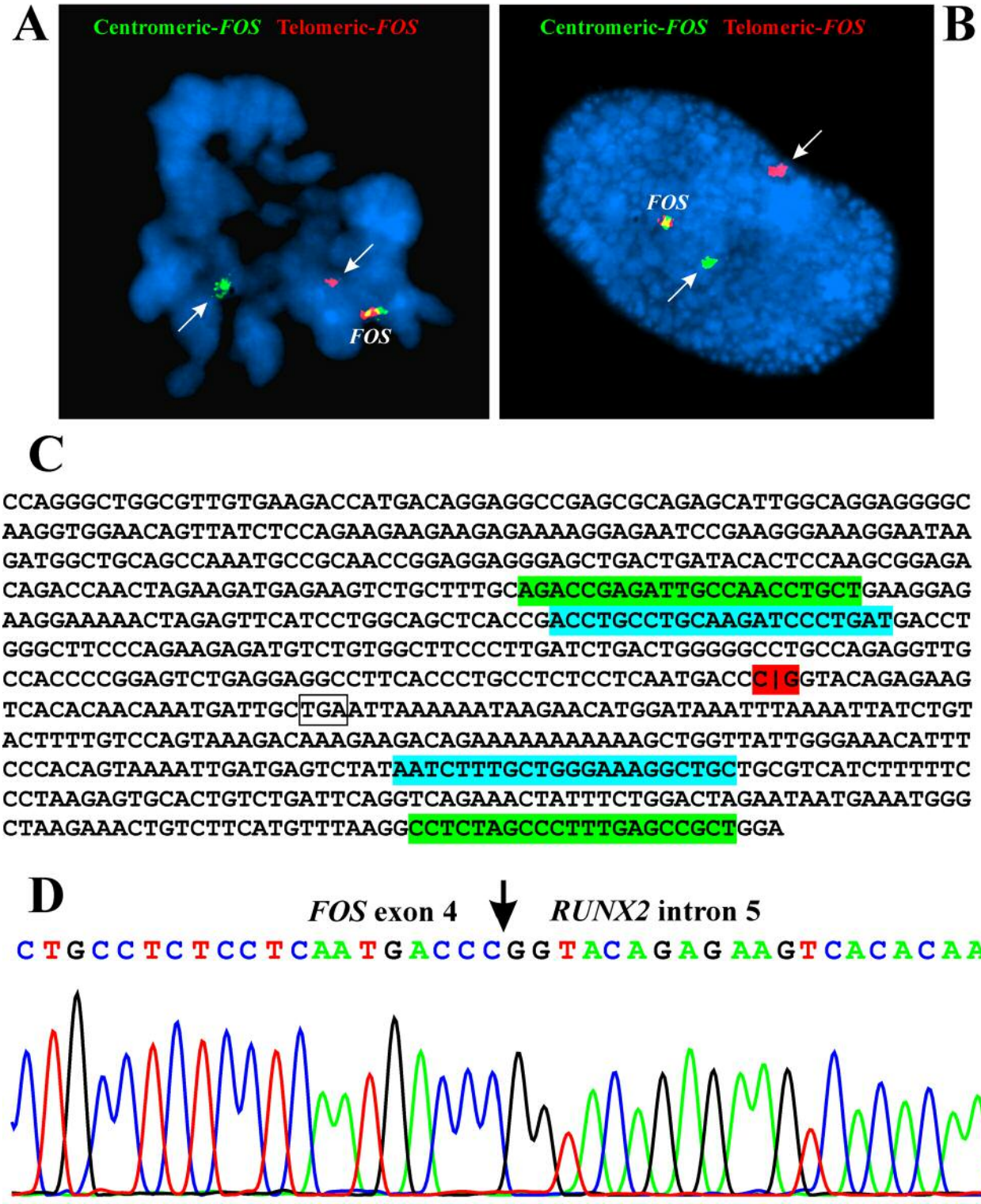

Figure 2. *Genetic analyses of the osteoblastoma of case 2. (A) Fluorescence in situ hybridization (FISH) on a metaphase plate with the FOS break-apart probe. (B) FISH on interphase nucleus with the FOS break-apart probe. (C) FOS-RUNX2 fusion sequence obtained from the raw data after RNA sequencing using the deFuse software package. The C|G junction of FOS with RUNX2 is highlighted in red. The position of the forward FOS-F3 and reverse RUNX2-R1 primers are highlighted in green. The position of the forward FOS-F4 and the reverse RUNX-R2 primers are highlighted in blue. (C) Partial sequence chromatogram of the cDNA amplified fragment showing the junction position of FOS with intron 5 of RUNX2.*

In tenosynovial giant cell tumors, chromosome aberrations, mainly translocations, disrupt the *CSF1* locus in 1p13 and replace the 3'-UTR of *CSF1* (exon 9 in sequence with accession number NM_000757) with new sequences contributed by the rearrangement partner (50-52). Exon 9 of *CSF1* mRNA (accession number NM-000575) contains microRNA targets (miRNA), a noncanonical G-quadruplex, and AU-rich elements (AREs) which control *CSF1* expression (53-56)

Thus, replacement of the expression-controling 3'-UTR region with a new sequence, often contributed by a translocation partner, appears to be a common pathogenetic theme shared by *FOS*, *HMGA2*, and *CSF1* and occurring particularly often in benign connective tissue tumors.

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, 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. IK performed the bioinformatic analyses. ML-I performed pathological examination. BB performed pathological examination. SH assisted with experimental design and writing of the article. All Authors read and approved of the final manuscript.

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