

# Updates on the cytogenetics and molecular cytogenetics of benign and intermediate soft tissue tumors (Review)

JUN NISHIO

Department of Orthopaedic Surgery, Faculty of Medicine, Fukuoka University, Fukuoka 814-0180, Japan

Received September 10, 2012; Accepted October 4, 2012

DOI: 10.3892/ol.2012.1002

**Abstract.** Soft tissue tumors are classified according to their histological resemblance to normal adult tissues and can be grouped into the following categories based on metastatic potential: benign, intermediate (locally aggressive), intermediate (rarely metastasizing) and malignant. Over the past two decades, considerable progress has been made in our understanding of the genetic background of soft tissue tumors. Traditional laboratory techniques, such as cytogenetic analysis and fluorescence *in situ* hybridization (FISH), can be used for diagnostic purposes in soft tissue pathology practice. Moreover, cytogenetic and molecular studies are often necessary for prognostics and follow-up of soft tissue sarcoma patients. This review provides updated information on the applicability of laboratory genetic testing in the diagnosis of benign and intermediate soft tissue tumors. These tumors include nodular fasciitis, chondroid lipoma, collagenous fibroma (desmoplastic fibroblastoma), giant cell tumor of tendon sheath (GCTTS)/pigmented villonodular synovitis (PVNS), angiofibroma of soft tissue, myxoinflammatory fibroblastic sarcoma (MIFS) and ossifying fibromyxoid tumor (OFMT).

tissue tumors are usually divided into benign, intermediate (locally aggressive), intermediate (rarely metastasizing) and malignant forms (1).

In current practice, cytogenetic and molecular cytogenetic [fluorescence *in situ* hybridization (FISH)] assays can serve as a useful diagnostic adjunct for soft tissue tumors. Many benign and intermediate soft tissue tumors are characterized by specific cytogenetic translocations or other rearrangements (2). This review provides updated information on the cytogenetic and molecular cytogenetic characteristics of benign and intermediate soft tissue tumors as well as their clinicopathological features, including nodular fasciitis, chondroid lipoma, collagenous fibroma (desmoplastic fibroblastoma), giant cell tumor of tendon sheath (GCTTS)/pigmented villonodular synovitis (PVNS), angiofibroma of soft tissue, myxoinflammatory fibroblastic sarcoma (MIFS) and ossifying fibromyxoid tumor (OFMT). The consistent genetic alterations are summarized in Table I.

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## 1. Introduction

Soft tissue tumors are a highly heterogeneous group of mesenchymal neoplasms that are classified according to the cell type they resemble. Within the various histogenetic categories, soft

## 2. Benign soft tissue tumors

Nodular fasciitis is a mass-forming, self-limited reactive process of unknown pathogenesis. It occurs in all age groups but more often in young adults. Males and females are about equally affected. Most nodular fasciitis arise in the subcutaneous tissues of the upper extremities (especially the volar aspect of the forearm), trunk and head and neck. Nodular fasciitis typically grows rapidly and reaches its final size within a few weeks. It usually measures  $\leq 2$  cm in its greatest dimension (1). Soreness, tenderness or slight pain may be present. Histologically, nodular fasciitis is composed of plump, immature-appearing fibroblasts and myofibroblasts lacking nuclear hyperchromasia and pleomorphism. Mitotic figures are fairly common, but atypical mitoses are virtually never evident (3). Due to its rapid growth, high cellularity and high mitotic activity, nodular fasciitis can be misdiagnosed as a malignant soft tissue tumor, especially fibrosarcoma or low-grade myxofibrosarcoma, often leading to unnecessarily aggressive therapy.

Clonal chromosomal aberrations have been detected by cytogenetic analysis in five cases of nodular fasciitis (4-8). Rearrangements involving 3q21 and 15q22-26 have been identified in a subset of nodular fasciitis. Velagaleti *et al* (8) suggested that *FGF7* and *NTRK3* are potential candidate target genes for the 15q rearrangement. A conventional

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*Correspondence to:* Dr Jun Nishio, Department of Orthopaedic Surgery, Faculty of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan  
E-mail: jnishio@cis.fukuoka-u.ac.jp

**Key words:** cytogenetics, molecular cytogenetics, soft tissue tumor

Table I. Chromosomal aberrations and associated molecular events in benign and intermediate soft tissue tumors.

Tumor type	Chromosomal aberration	Molecular event
Benign		
Nodular fasciitis	Not assigned	<i>USP6</i> rearrangement <sup>a</sup>
	3q21 rearrangement	Not known
	15q22-26 rearrangement	Not known
Chondroid lipoma	t(11;16)(q13;p13)	<i>C11orf95-MKL2</i>
Collagenous fibroma	11q12 rearrangement <sup>b</sup>	<i>FOSL1</i> rearrangement
GCTTS/PVNS	1p11-13 rearrangement <sup>c</sup>	<i>CSF1</i> rearrangement
	16q24 rearrangement	Not known
	Trisomy 5 and/or trisomy 7	Not known
Angiofibroma of soft tissue	t(5;8)(p15;q13)	<i>AHRR-NCOA2</i>
Intermediate (locally metastasizing)		
MIFS <sup>d</sup>	t(1;10)(p22;q24)	<i>TGFBR3, MGEA5</i> rearrangement
Ossifying fibromyxoid tumor	6p21 rearrangement <sup>e</sup>	<i>PHF1</i> rearrangement

<sup>a</sup>*MYH9-USP6* fusion gene is identified in a subset of nodular fasciitis. <sup>b</sup>Most preferred rearrangement is t(2;11)(q31;q12). <sup>c</sup>Most preferred rearrangement is t(1;2)(p11-13;q35-37) resulting in a *COL6A3-CSF1* fusion gene. <sup>d</sup>Ring or marker chromosome, composed of amplified 3p12, is associated with an increased expression of *VGLL3*. <sup>e</sup>Most preferred rearrangement is t(6;12)(p21;q24) resulting in an *EP400-PHF1* fusion gene. GCTTS/PVNS, giant cell tumor of tendon sheath/pigmented villonodular synovitis; MIFS, myxoinflammatory fibroblastic sarcoma.

comparative genomic hybridization (CGH) study has revealed gains of 10p14-15 and 20q12-13.3 in only one of five nodular fasciitis cases (9). A gene expression analysis has shown higher expression of the *SYK*, *LYN*, *EPHA4*, *OAS1*, *TCF20*, *MITF*, *CXCL9*, *CXCL10*, *MMP1*, *MMP9*, *MMP13*, *CTSC*, *CTSL* and *PLAU* genes (10). Bacac *et al* (10) suggested that nodular fasciitis and desmoid-type fibromatosis may be distinguished on the basis of the expression profile of several gene clusters.

More recently, Erickson-Johnson *et al* (11) reported that *USP6* rearrangements with the formation of the fusion gene *MYH9-USP6* occur in most examples of nodular fasciitis. *USP6* is located on chromosome 17p13 and has a limited expression in normal cells. *USP6* rearrangements were first identified in aneurysmal bone cyst (ABC) (12). The presence of *USP6* rearrangements has also been reported in two cases of ABC-like myositis ossificans (13). However, *USP6* rearrangements are absent in its histological mimics in soft tissue, including desmoid-type fibromatosis, fibrosarcoma and myxofibrosarcoma. Therefore, *USP6* FISH is an extremely useful adjunct in the diagnosis of nodular fasciitis.

Chondroid lipoma, despite its worrisome histological appearance, is a benign soft tissue tumor with features of both embryonal fat and embryonal cartilage (14). It usually occurs in the third or fourth decade of life with a female predominance. The tumor typically presents as a slow-growing, painless mass in the proximal extremities and limb girdles. Most chondroid lipomas measure 2-7 cm in their greatest dimension (1). Chondroid lipoma is often deep seated, involving skeletal muscle or deep fibrous connective tissues. Histologically, chondroid lipoma has a lobular pattern and consists of sheets, nests and cords of round cells embedded in a myxoid to hyalinized chondroid matrix, with a variable amount of mature adipose tissue. The cells show cytoplasmic vacuolation or eosinophilic granular cytoplasm. Significant nuclear pleomorphism

or mitotic activity is not evident. Chondroid lipoma may be mistaken for a malignant soft tissue tumor, especially myxoid liposarcoma or extraskeletal myxoid chondrosarcoma (15,16).

An identical reciprocal translocation, t(11;16)(q13;p13), has been detected by cytogenetic analysis in six cases of chondroid lipoma (17-20). Recurrent involvement of 11q13 has also been described in hibernoma, but not in association with 16p13 (15).

In their study, Huang *et al* (20) reported that the t(11;16)(q13;p13) translocation results in a fusion of *C11orf95* and *MKL2*. These gene rearrangements have not been identified in other soft tissue tumors thus far, and appear to be characteristic for chondroid lipoma. FISH assay for *C11orf95* or *MKL2* rearrangements is therefore useful for the differential diagnosis of chondroid lipoma and its histological mimics, particularly when evaluating small samples (20).

Collagenous fibroma, also known as desmoplastic fibroblastoma, is a benign fibrous soft tissue tumor first described by Evans (21) in 1995. This tumor primarily occurs in the subcutaneous tissues or skeletal muscle of upper extremities and has a peak incidence in the fifth to seventh decades of life with a male predominance. Few cases have been encountered in children (22,23). Collagenous fibroma typically presents as a firm, slow-growing, painless mass, measuring  $\leq 4$  cm in its greatest dimension (3). Grossly, collagenous fibroma appears as a well-circumscribed mass with a white to gray cut surface (Fig. 1A). Histologically, the lesion is hypocellular and consists of spindle- to stellate-shaped cells embedded in a collagenous or myxocollagenous stroma (Fig. 1B). Mitotic figures are rare or absent and necrosis is not present. Collagenous fibroma may be mistaken for several other benign and low-grade malignant soft tissue tumors, including desmoid-type fibromatosis and low-grade fibromyxoid sarcoma.

Clonal chromosomal aberrations have been detected by cytogenetic analysis in 10 cases of collagenous fibroma

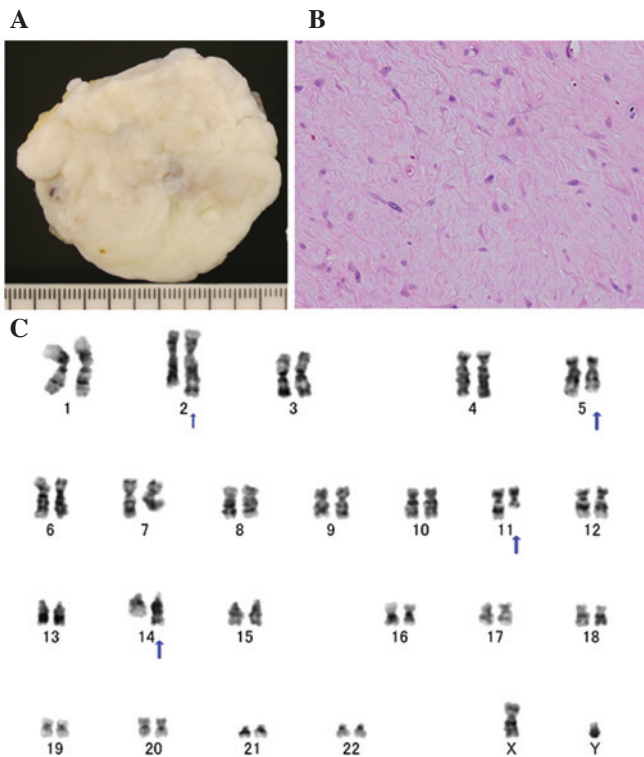


Figure 1. Collagenous fibroma. (A) Gross appearance showing a well-circumscribed mass with a gray-white cut surface. (B) The tumor is composed of spindle- to stellate-shaped cells in a dense collagenous stroma. (C) G-banded karyotype showing a 2;11 translocation. A t(5;14)(q15;q22) translocation is evident. Arrows indicate the structural chromosome aberrations.

(24-29). The long arm of chromosome 11, in particular 11q12, is involved in all cases except one (Fig. 1C). Several chromosomal segments have been recognized as translocation partners to 11q12 and the most preferred rearrangement is t(2;11)(q31;q12). Notably, the same translocation has also been observed in a case of fibroma of tendon sheath (30), suggesting a pathogenetic link between these two entities.

Macchia *et al* (29) recently reported that *FOSL1* (formerly known as *Fra-1*) is a candidate target gene for 11q12 rearrangements in collagenous fibroma. This gene is a member of the Fos family and encodes leucine zipper proteins. *FOSL1* has been reported to be activated in multiple human carcinomas, including lung, colon, breast, prostate, brain and head and neck cancers (31). However, *FOSL1* rearrangements have not been detected in other soft tissue tumors thus far. *FOSL1* FISH may therefore be important in the diagnosis of collagenous fibroma.

Tenosynovial giant cell tumor is classified into two types, with different clinical features and biological behavior, although their histological finding is similar (1). The localized type, also known as GCTTS, may occur at any age but has a peak incidence in the third to fourth decades of life with a female predominance. GCTTS usually presents as a painless, slow-growing mass in the extremities, especially the fingers. Grossly, GCTTS is well circumscribed and encapsulated. Recurrences are non-destructive and are easily controlled by re-excision. The diffuse type, also known as PVNS, tends to occur in younger patients and is slightly more common in females. PVNS usually presents as a painful, longstanding mass with hemarthrosis in large joints,

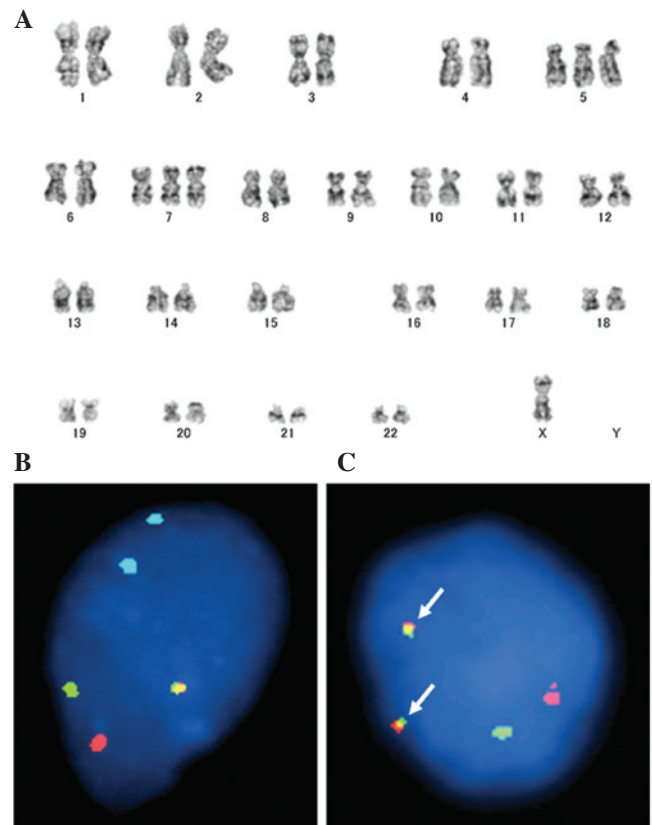


Figure 2. Pigmented villonodular synovitis. (A) G-banded karyotype showing the presence of an extra copy of chromosomes 5 and 7. (B) Fluorescence *in situ* hybridization (FISH) analysis with custom-designed probes flanking the *CSF1* gene (proximal, orange; distal, green) shows a split of the orange and green signals, indicating disruption of *CSF1*. The aqua signals represent the centromeric region of the chromosome 7 homologues. (C) FISH analysis with custom-designed probes spanning the *CSF1* (green) and *COL6A3* (orange) genes shows overlapping yellow signals (arrows), confirming the presence of a *COL6A3-CSF1* fusion.

especially the knee. Grossly, PVNS is poorly circumscribed and has a prominent villonodular growth pattern. This potentially aggressive lesion frequently recurs, occasionally necessitating radical surgery (1). Histologically, the lesion is composed of sheets of round or polygonal cells admixed with multinucleated giant cells and xanthoma cells with hemosiderin granules. Compared with GCTTS, cleft-like or pseudoglandular spaces are more prominent in PVNS. Mitotic activity is usually present, but atypical mitoses and nuclear atypia are not evident.

Clonal chromosomal aberrations have been detected by cytogenetic analysis in 45 cases of GCTTS/PVNS (32-45). GCTTS/PVNS exhibits mostly simple karyotypes characterized by one or a few chromosomal rearrangements or numerical aberrations. The short arm of chromosome 1, in particular 1p11-13, is frequently involved in GCTTS/PVNS. Several chromosomal segments have been recognized as translocation partners to 1p11-13 and the most preferred rearrangement is t(1;2)(p11-13;q35-37) resulting in a *COL6A3-CSF1* fusion gene (46,47). In addition, another possible cytogenetic subgroup might be characterized by translocations involving 16q24. Moreover, trisomy for chromosomes 5 and/or 7, usually as the sole anomaly, has been observed only in PVNS (Fig. 2A).

In a previous study, West *et al* (46) demonstrated that *CSF1* at 1p13 is often rearranged in GCTTS/PVNS. The authors

also detected high levels of its receptor (CSF1R) expression in most of the cells. However, only a minority of tumor cells (2-16%) carry the translocation and express CSF1. These findings suggest that aberrant CSF1 signaling is crucial in the pathogenesis of GCTTS/PVNS. *CSF1* rearrangements can be detected by FISH (Fig. 2B and C), although probes are not yet commercially available.

Blay *et al* (48) initially reported a case of recurrent PVNS showing a complete response after imatinib therapy. More recently, Cassier *et al* (49) reported that the overall response rate of a daily dose of imatinib (400 mg) in patients with locally advanced/metastatic PVNS was 19%. Moreover, the overall symptomatic response rate was 73%. These results suggest that the use of targeted inhibitors of CSF1R, such as imatinib, are a good therapeutic option in the treatment strategy of locally advanced/metastatic or recurrent PVNS.

Angiofibroma of soft tissue is a distinctive benign fibrovascular soft tissue tumor first described by Mariño-Enríquez and Fletcher (50) in 2012. It usually occurs in middle-aged adults, with a female predominance. Angiofibroma of soft tissue typically presents as a slow-growing, painless, well-defined mass in the extremities, often in relationship to joints or fibrotendinous structures. The lesions range from 1.2 to 12 cm in their greatest dimension, with a median size of 3.5 cm (50). Histologically, the tumor consists of a proliferation of relatively uniform, bland spindle cells set in a variably myxoid-to collagenous stroma with a prominent and complex vascular pattern. Mitotic activity is occasionally observed, but cytologic atypia and nuclear hyperchromasia are absent. Immunohistochemically, the neoplastic cells are focally positive for epithelial membrane antigen. Occasional cases may show scattered cells that stain CD34, smooth muscle actin and desmin. Angiofibroma of soft tissue may be mistaken for a number of benign and low-grade malignant soft tissue tumors, including cellular angiofibroma, solitary fibrous tumor, low-grade fibromyxoid sarcoma, low-grade myxofibrosarcoma and myxoid liposarcoma (50).

Clonal chromosomal aberrations have been detected by cytogenetic analysis in seven cases of soft tissue angiofibroma (50-52). A reciprocal translocation, t(5;8)(p15;q13), has been identified in five cases. A three-way t(5;8;8)(p15;q13;p11) translocation has also been described in one case (50). A gene expression analysis has shown higher expression of *CYP11A1* in angiofibroma of soft tissue compared with myxofibrosarcoma (51).

In their study, Jin *et al* (51) reported that the t(5;8)(p15;q13) translocation results in a fusion of *AHRR* and *NCOA2*. *AHRR* is located on chromosome 5p15 and is not involved in gene fusions. *NCOA2* is located on chromosome 8q13 and has been identified as the 3'-partner in fusions with *PAX3* and *HEY1* in soft tissue sarcomas (53,54). However, these gene rearrangements have not been detected in its histological mimics. FISH assay for *AHRR* or *NCOA2* rearrangements can therefore be applied as a reliable laboratory test in the diagnosis of soft tissue angiofibroma.

### 3. Intermediate soft tissue tumors

MIFS is an intermediate (rarely metastasizing) soft tissue tumor first described by Montgomery *et al* (55) in 1998.

It primarily occurs in the subcutaneous tissues of distal extremities and has a peak incidence in the fourth and fifth decades of life with no gender predilection. MIFS typically presents as a slow-growing, painless, poorly defined mass. The preoperative diagnosis in most cases is benign and may include tenosynovitis, ganglion cyst and GCTTS/PVNS (1). Histologically, MIFS is multinodular, poorly circumscribed and characterized by a prominent myxoid matrix containing numerous inflammatory cells, including lymphocytes, plasma cells, neutrophils and eosinophils (56). Germinal centers are occasionally encountered. Neoplastic cells include spindle-shaped and epithelioid cells with mild to moderate nuclear atypia, large polygonal and bizarre ganglion-like cells, Reed-Sternberg-like cells with huge inclusion-like nucleoli and multivacuolated lipoblast-like cells. Hemosiderin deposition may be evident. Mitotic activity is usually low and necrosis is rarely present. Immunohistochemically, the neoplastic cells are diffusely positive for vimentin and focally for CD68 and CD34. Occasional cases may show scattered cells that stain for cytokeratin or smooth muscle actin. More importantly, immunostains for leukocyte common antigens, CD15 and CD30, are negative (16). MIFS can be histologically mistaken for a number of benign and malignant soft tissue tumors, including GCTTS/PVNS, inflammatory myofibroblastic tumor and myxofibrosarcoma.

Clonal chromosomal aberrations have been detected by cytogenetic analysis in 10 cases of MIFS and hybrid MIFS/hemosiderotic fibrolipomatous tumor (HFLT) (57-63). Cytogenetic and molecular cytogenetic studies have identified the frequent presence of a balanced or unbalanced t(1;10)(p22;q24) translocation and ring or marker chromosomes secondary to 3p11-12 amplifications. A reciprocal t(2;6)(q31;p21.3) translocation has also been described as the sole anomaly in a single case (59). It is of interest that the t(1;10) translocation has also been identified in three cases of pure HFLT (61,63,64). These findings suggest that MIFS and HFLT likely represent different morphologic variants of the same entity.

Conventional and array CGH studies have shown the amplification of 3p11-12 (61,65). Notably, Hallor *et al* (61) demonstrated that 3p11-12 amplification is associated with an increased expression of *VGLL3* and *CHMP2B*. Moreover, Antonescu *et al* (63) confirmed the presence of high level *VGLL3* amplification by FISH in MIFS, as well as in HFLT and cases with hybrid morphology. *VGLL3* has been shown to be amplified and overexpressed in undifferentiated pleomorphic sarcoma and dedifferentiated liposarcoma (66). These findings suggest that *VGLL3* is the main target of 3p12 amplification and this genetic event may be crucial in the development and progression of certain subsets of soft tissue sarcomas. A gene expression analysis has shown overexpression of *NPM3* and particularly *FGF8* (61). These two genes have been mapped to 10q24. *FGF8* is a member of the fibroblast growth factor family. *FGF8* overexpression has been shown to increase tumor growth and angiogenesis (67).

Antonescu *et al* (63) reported that FISH analysis for *TGFBR3* at 1p22 and *MGEA5* at 10q24 rearrangements can be applied as a reliable molecular test in the diagnosis of MIFS.

According to the current World Health Organization classification, OFMT is an intermediate (rarely metastasizing) soft



tissue tumor of uncertain lineage (1). The biological behavior of OFMT varies. OFMT primarily occurs in the extremities, trunk and head and neck of adults with a median age of approximately 50 years (68-70). Males are affected more frequently than females. OFMT typically presents as a slow-growing, painless, well-defined, subcutaneous mass. The lesions range from 1 to 20 cm in their greatest dimension, with a median size of 3-5 cm (68-70). Histologically, OFMT is composed of uniform round, ovoid, or spindle-shaped cells arranged in nests and cords and deposited in a variably fibromyxoid stroma. In approximately 80% of cases, there is an incomplete shell of lamellar bone found at the periphery of the nodules (3). Small foci of calcification and metaplastic cartilage are also evident. Mitotic activity is usually less than 1/10 high power fields. Although a majority of OFMTs are histologically benign and show correspondingly benign clinical behavior, it has been recognized that a subset of OFMTs have atypical histological findings, such as high cellularity and/or increased mitotic activity and show correspondingly more aggressive clinical behavior (68,70). Immunohistochemically, the neoplastic cells are typically positive for vimentin and S-100 protein. The cells may also express desmin, CD10, Leu-7, neuron-specific enolase and glial fibrillary acidic protein. OFMT may be mistaken for a number of benign and malignant soft tissue tumors, including chondroid syringoma, low-grade fibromyxoid sarcoma and extraskeletal osteosarcoma.

Clonal chromosomal aberrations have been detected by cytogenetic analysis in seven cases of OFMT (68,71-74). The short arm of chromosome 6, in particular 6p21, is frequently involved in OFMT. Notably, a balanced or unbalanced t(6;12) (p21;q24) translocation appears to be characteristic for OFMT. A gene expression analysis has shown overexpression of *EAAT4* and underexpression of *PMP22* in OFMT compared with nerve sheath myxoma and schwannoma (70). Moreover, Graham *et al* (70) identified loss of *INI-1* at 22q11.2 in five of seven cases by interphase FISH.

Gebre-Medhin *et al* (74) recently reported that *PHF1* at 6p21 is frequently rearranged in OFMT, including atypical and malignant variants. Moreover, *PHF1* was fused to *EP400* at 12q24 in one atypical case with the t(6;12) translocation. OFMT is the second neoplasm, in addition to endometrial stromal tumor, in which *PHF1* is involved in fusions with ectopic sequences. These findings suggest that FISH assay for *PHF1* rearrangements serves as an excellent diagnostic tool in ambiguous cases.

#### 4. Conclusions

Traditional laboratory techniques, such as cytogenetic analysis and FISH, have a pivotal role in the diagnosis of soft tissue tumors. Over the past few years, some novel gene rearrangements have been described in benign and intermediate soft tissue tumors. Notably, the t(5;8)(p15;q13) translocation, resulting in the *AHRR-NCOA2* fusion gene, was identified in angiofibroma of soft tissue recently proposed as a new clinicopathologic entity (51). FISH can be used to distinguish between entities with similar histological appearances, although probes are not yet commercially available. Understanding the basis of these ancillary techniques and their application is critical to provide accurate diagnoses of soft tissue tumors.

#### Acknowledgements

This study was supported in part by Fukuoka Cancer Society, Ogata Foundation and the Foundation for the Promotion of Medical Science.

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