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ONCOLOGY: *Diagnostic Biomarkers in Bone & Soft Tissue Tumors – Part I*

Abbreviations: FISH: fluorescence in situ hybridization, GIST: gastrointestinal stromal tumor, IHC: immunohistochemistry, ITD: internal tandem duplication, LOF: loss-of-function, NGS: next-generation sequencing, PCR: polymerase chain reaction, RT-PCR: reverse transcriptase polymerase chain reaction, RTK: receptor tyrosine kinase

Differentiation	Entity	Gene(s)	Type	Assays	Notes
Adipocytic	Ordinary lipoma	*HMGA2/HMGA1*	Fusions	FISH, NGS	*HMGA2* rearrangements are not specific
	Angiolipoma	*PRKD2*	Mutations (activating)	NGS	80%
	Spindle cell/pleomorphic lipoma	*RB1*	Deletion/Loss	FISH, IHC, NGS	IHC: Rb loss
	Hibernoma	*MEN1, AIP*	Co Deletion/Loss	FISH	11q13
	Lipoblastoma	*PLAG1*	Rearrangements	FISH, NGS	Partners: *HAS2*, numerous others reported
	Chondroid lipoma	*ZFTA::MRTFB*	Fusion	FISH, NGS	
	Atypical lipomatous tumor Well-differentiated liposarcoma Dedifferentiated liposarcoma	*MDM2*	Amplification	IHC, FISH, NGS	*MDM2, CDK4, HMGA2, SAS, GLI* (12q14-15) often coamplified(1); *HMGA2* rearrangements and amplification common
	Myxoid liposarcoma Round cell liposarcoma	*FUS::DDIT3* *EWSR1::DDIT3 (1)*	Fusions	FISH, NGS	*EWSR1-DDIT3* in <5% *TERT* promoter mutations in 60%
(Myo)Fibroblastic	Nodular fasciitis*	*USP6*	Fusions	FISH, NGS	*MYH9* most common partner for nodular fasciitis
	Fibrous hamartoma of infancy	*EGFR*	Exon 20 insertions	NGS, PCR	
	Desmoplastic fibroblastoma	*FOSL1, FOS1 (less common)*	Rearrangements	IHC, FISH	IHC: Strong, diffuse nuclear FOSL1
	Myofibroblastoma	*RB1*	Deletion/Loss	FISH, IHC, NGS	IHC: Rb loss
	Cellular angiofibroma	*RB1*	Deletion/Loss	FISH, IHC, NGS	IHC: Rb loss
	Superficial acral fibromyxoma	*RB1*	Deletion/Loss	FISH, IHC, NGS	IHC: Rb loss
	Calcifying aponeurotic fibroma	*FN1::EGF*	Fusions	NGS	
	EWSR1::SMAD3 fibroblastic tumor	*EWSR1::SMAD3*	Fusions	FISH, NGS	
	Superficial CD34+ fibroblastic tumor	*PRDM10*	Fusions	FISH, NGS	Emerging data; partners: *MED12, CITED2*
	Angiofibroma of soft tissue	*AHRR::NCOA2*	Fusions	NGS	*AHRR::NCOA3* (less common); reports of other rare fusions
	Tenosynovial giant cell tumor/pigmented villonodular synovitis	*CSF1*	Rearrangements	FISH, NGS	Only rare neoplastic cells. CSF1R targeted therapy available (1).
	Deep benign fibrous histiocytoma	*PRKCB, PRKCD*	Fusions	FISH, NGS	20% with *PRKC* fusions
	Desmoid-type fibromatosis	*CTNNB1* (sporadic)	Mutations (activating)	NGS, IHC	Nuclear staining; Trisomy 8 or 20; loss of 5q21 (1)
		APC (FAP-related)	Mutations (LOF)	NGS	
	Lipofibromatosis	*EGF, EGFR, ROS1, RET, PDGFRB*	Fusions	NGS, FISH	Several including *EGF* and similar ligands as well as receptor tyrosine kinases (*FN1-EGF* most common)
	Giant cell fibroblastoma	*COL1A1::PDGFB*	Fusions	FISH, NGS	
	Dermatofibrosarcoma protuberans	*COL1A1::PDGFB* *PDGFD fusions*	Fusions	FISH, NGS	Tyrosine kinase inhibitor therapy available (1); 96-98% with *COL1A1::PDGFB* and 1-2% with PDGFD fusions (3)
	Solitary fibrous tumor	*NAB2::STAT6*	Fusions	IHC, NGS	(1)
	Inflammatory myofibroblastic tumor	*TPM3::ALK6* *TPM4::ALK6* *CLTC::ALK6*	Fusions	FISH, IHC, NGS	Many partners, subset with *ROS1, NTRK3* Rare cases with *RET, PDGFRB*. ALK- and NTRK-targeted therapy available (1)

(Myo)Fibroblastic (cont.)		*RANBP2::ALK6* *CARS::ALK6* *ATIC::ALK6* *ETV6::NTRK3* *TFG::ROS1*			
	Congenital/Infantile fibrosarcoma	*ETV6::NTRK3 (1)*	Fusions	FISH, IHC, NGS	Fusions in *BRAF, NTRK1, MET* in minor subset. *BRAF* intragenic rearrangements rarely. NTRK-targeted therapy available
	Low-grade fibromyxoid sarcoma (LGFMS)**	*FUS::CREB3L2* *FUS::CREB3L1 (1)*	Fusions	FISH, IHC, NGS	IHC: MUC4 positive Rare cases with *FUS::CREB3L1*, *EWSR1::CREB3L1*
	Sclerosing epithelioid fibrosarcoma (SEF)**	*EWSR1::CREB3L1*	Fusions	FISH, IHC, NGS	IHC: MUC4+; *YAP1*, *KMT2A* fusions in a MUC4-neg subset showing overlap between LGFMS and SEF
Pericytic	Myopericytoma/myofibroma	*PDGFRB*	Mutations	NGS	70% (3)
		SRF::RELA	Fusions	NGS, FISH	20-30%; Cellular/atypical myofibromas (3)
	Glomus tumor	*NOTCH*	Fusions	NGS	*CARMN::NOTCH (70-80%) (3); MIR143* fusions with *NOTCH1, NOTCH2, NOTCH3*
		BRAF, KRAS	Mutations	NGS	Small subset; *BRAF* V600E: 6% (3)
Skeletal Muscle	Alveolar rhabdomyosarcoma	*PAX3::FOXO1* *PAX7::FOXO1* *PAX3::AFX*	Fusions	FISH, NGS	(1)
	Spindle cell/sclerosing rhabdomyosarcoma	*VGLL2, SRF, TEAD 1, NCOA2, CITED2*	Fusions	FISH, NGS	Infantile cases (<1 year), various fusions
		MYOD1	L122R mutation	NGS	Older patients
		EWSR1, FUS, NCOA2	Fusions	FISH, NGS	Intraosseous spindle cell rhabdomyosarcoma
Vascular	Anastomosing hemangioma	*GNAQ, GNA14*	Mutations (activating)	NGS	
	Epithelioid hemangioma	*FOS, FOSB*	Fusions	FISH, NGS	
	Pseudomyogenic hemangioendothelioma	*FOSB*	Fusions	FISH, NGS	*SERPINE* and *ACTB* are common partners
	Epithelioid hemangioendothelioma	*WWTR1::CAMTA1* *YAP1::TFE3*	Fusions	FISH, IHC, NGS	*(1) YAP1-TFE3* in a small subset
GIST	Sporadic GIST	*KIT, PDGFRA*	Mutations (activating)	NGS	75% *KIT* mutant, 10% *PDGFRA mutant*. Tyrosine kinase inhibitor therapy available (2)
	Succinate dehydrogenase-deficient GIST	*SDHA, SDHB, SDHC, SDHD*	Mutations (LOF)	NGS, IHC	5-10% of cases, IHC: SDHB negative
Uncertain	NTRK-rearranged spindle cell neoplasm (emerging)	*NTRK1, NTRK2, NTRK3*	Fusions	FISH, NGS	Most tumors harbor *NTRK1* fusions with a variety of partners

**USP6* fusions with various partners have also been reported in proliferative fasciitis/myositis, cranial fasciitis, myositis ossificans, fibroma of tendon sheath, and fibro-osseous pseudotumor of digit; all are thought to be related entities.

** Some cases show morphologic overlap between low-grade fibromyxoid sarcoma (LGFMS) and sclerosing epithelioid fibrosarcoma; these cases generally show *FUS-CREB3L2* fusions.

Note: Not all of the biomarkers above are diagnostically useful currently, and none (with rare exceptions) are completely specific.

***References*:**

1. National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Soft Tissue Sarcoma Version 2.2023– April 25,2023 NCCN.org. *accessed 7/23/2023*
2. National Comprehensive Cancer Network. Clinical practice Guidelines in Oncology. Gastrointestinal Stromal Tumors Version 1.2023 — March 13, 2023, NCCN.org. *accessed* 7/23/3023.
3. Semin Diagn Pathol (2023) 40(4):246-257, PMID: 37156707.