HHS Public Access

Author manuscript

Genes Chromosomes Cancer. Author manuscript; available in PMC 2016 September 06.

Published in final edited form as:

Genes Chromosomes Cancer. 2016 April ; 55(4): 291–310. doi:10.1002/gcc.22335.

Gene Fusions in Soft Tissue Tumors: Recurrent and Overlapping Pathogenetic Themes

Fredrik Mertens[*,1], **Cristina R. Antonescu**[2], and **Felix Mitelman**[1]

[1]Department of Clinical Genetics, University and Regional Laboratories, Lund University, Lund, Sweden

[2]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Gene fusions have been described in approximately one-third of soft tissue tumors (STT); of the 142 different fusions that have been reported, more than half are recurrent in the same histologic subtype. These gene fusions constitute pivotal driver mutations, and detailed studies of their cellular effects have provided important knowledge about pathogenetic mechanisms in STT. Furthermore, most fusions are strongly associated with a particular histotype, serving as ideal molecular diagnostic markers. In recent years, it has also become apparent that some chimeric proteins, directly or indirectly, constitute excellent treatment targets, making the detection of gene fusions in STT ever more important. Indeed, pharmacological treatment of STT displaying fusions that activate protein kinases, such as ALK and ROS1, or growth factors, such as PDGFB, is already in clinical use. However, the vast majority (52/78) of recurrent gene fusions create structurally altered and/or deregulated transcription factors, and a small but growing subset develops through rearranged chromatin regulators. The present review provides an overview of the spectrum of currently recognized gene fusions in STT, and, on the basis of the protein class involved, the mechanisms by which they exert their oncogenic effect are discussed.

GENE FUSIONS ARE IMPORTANT DRIVER MUTATIONS IN SOFT TISSUE TUMORS

Gene fusions, i.e., the juxtapositioning of two genes leading to the translation of a deregulated and/or chimeric protein, have been described in all major types of neoplasia, including benign as well as malignant tumors of hematologic, epithelial, and mesenchymal origin (Mertens et al., 2015; Mitelman et al., 2015). While some of the fusions appear to be passenger mutations caused by the increased genetic instability that is a hallmark of many malignant neoplasms, others constitute strong driver alterations (Mertens et al., 2015; Yoshihara et al., 2015). Similar to other types of mutation, the classification of a gene fusion as driver or passenger mutation can be achieved through careful evaluation in experimental models, but strong indirect support for a significant pathogenetic role is also suggested when

[*]Correspondence to: Fredrik Mertens, Department of Clinical Genetics, University and Regional Laboratories, Lund University, SE-221 85 Lund, Sweden. fredrik.mertens@med.lu.se.

a certain gene fusion is recurrent, by revealing that it is associated with relatively few other mutations, or by establishing that it is restricted to one or a few morphologic subtypes.

The characterization of neoplasia-associated gene fusions has increased our general understanding of fundamental pathogenetic mechanisms as well as improved patient management through refined tumor classification and stratification, thus being highly rewarding for scientists and clinicians dealing with the clinically heterogeneous group of neoplasms known as soft tissue tumors (STT). STT currently encompass more than 100 separate morphologic entities (Fletcher et al., 2013), many of which are exceedingly rare and thus require review by expert soft tissue pathologists for a correct classification. In addition, an increasing number of STT patients is considered for neoadjuvant treatment, further increasing the need for a precise diagnosis (Linch et al., 2014; Reichardt, 2014). Still, even highly experienced pathologists with access to an extensive battery of immunohisto-chemical (IHC) markers sometimes face differential diagnostic challenges; in such cases, genetic analyses investigating the presence of particular gene fusions may prove pivotal (Antonescu and Dal Cin, 2014). In the early 1980s, when characteristic chromosomal aberrations were first detected in STT, it emerged that certain subtypes display one or more recurrent, often pathognomonic, structural chromosome aberrations, notably translocations. With time, these rearrangements could be characterized at the molecular level, revealing that they often result in a gene fusion (Mitelman et al., 2007). Once the molecular genetic correlates of the chromosomal aberrations were established, they became identifiable also by directed analyses such as fluorescence in situ hybridization (FISH) or RT-PCR. Moreover, formalin-fixed paraffin-embedded tissue could now be used for their detection, thus increasing the number of cases that could be tested and circumventing the need for fresh tumor material. In recent years, the identification of gene fusions has been further improved by the introduction of next-generation sequencing (NGS) tools, in the clinic as well as in the research setting (Mertens and Tayebwa, 2014; Mertens et al., 2015).

During the last two decades—starting with the *EWSR1-FLI1* fusion in Ewing sarcoma in 1992 (Delattre et al., 1992)—142 different gene fusions have been identified in STT, revealing pathogenetic mechanisms that involve a variety of different genes and pathways. These fusions have become highly useful diagnostic tools, either as such or by providing a rationale for novel IHC markers (Hornick, 2014). Furthermore, the molecular characterization has revealed new pathways in tumorigenesis and disclosed unexpected molecular links among different subtypes of STT or with carcinomas, lymphomas, and leukemias. While there are recent reviews on general (Mertens et al., 2015), technological (Mertens and Tayebwa, 2014), or clinical (Antonescu and Dal Cin, 2014) aspects of gene fusions in STT and other neoplasms, a comprehensive review of their biological features is missing. Hence, the current review aims at presenting the distribution of gene fusions among different morphologic subtypes, examine the types of gene involved and how they interact with each other, and provide an overview of patho-genetic mechanisms in these STT.

DISTRIBUTION OF GENE FUSIONS IN STT

The Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer (Mitelman et al., 2015) was queried on September 24, 2015 for gene fusions reported in

tumors that are included in the latest WHO classification of soft tissue and bone tumors and that originated in soft tissues (Fletcher et al., 2013). In addition, three recently delineated STT—pericytoma with t(7;12), angiofibroma of soft tissue, and biphenotypic sinonasal sarcoma—were included (Dahlén et al., 2004; Mariño-Enriquez and Fletcher, 2012; Wang et al., 2014). Using these criteria, gene fusions were found in 40 different tumor types, representing all major subgroups except smooth muscle tumors, gastrointestinal stromal tumors, and peripheral nerve sheath tumors (Table 1). All chromosomes except the Y chromosome are involved, but with a distinctly non-random distribution of affected gene loci (Fig. 1). For instance, six separate genes (*ATF1*, *DDIT2*, *GLI1*, *HMGA2*, *NAB2*, and *STAT6*) that map to chromosome bands 12q13-q15 are recurrently involved in different types of STT; in addition, there are numerous nonrecurrent gene fusions affecting other genes in chromosome arm 12q, typically resulting from the intrachromosomal rearrangements that are associated with the amplification events that are characteristic for certain subtypes of STT (Table 1). Otherwise, there is a relative lack of gene fusions occurring through intrachromosomal rearrangements in STT, probably reflecting the fact that these tumors remain poorly investigated by NGS techniques (Mertens and Tayebwa, 2014). Indeed, several recurrent gene fusions that were recently detected by NGS, such as the *NAB2-STAT6* fusion in solitary fibrous tumor, strongly suggest that fusions of neighboring genes are pathogenetically significant also in STT (Chmielecki et al., 2013; Mohajeri et al., 2013; Robinson et al., 2013).

A total of 142 different gene fusions were found, 78 of which have been reported in at least two cases of the same morphological STT subtype and are here defined as recurrent; these gene fusions and references to the studies in which they were first described are given in Table 2. Recurrent gene fusions seem to be particularly prevalent among tumors of uncertain differentiation or histo-genesis, involving close to half of the tumor types (Table 1). However, it should be emphasized that many of the gene fusions were only very recently described, and their association(s) with different morphologic subtypes remains poorly explored. Furthermore, several of the gene fusions so far described only in single cases will undoubtedly become recurrent in the near future. Attempts were also made to estimate, on the basis of all available literature data, the frequency of each recurrent gene fusion (Table 2). Gene fusions estimated to occur in at least 10% of a specific STT are indicated in bold in Table 1.

Why have gene fusions been reported in only one-third of all STT subtypes? In general, the absence or presence of gene fusions is not related to basic clinicopathologic features such as grade of malignancy or degree of differentiation: gene fusions may be found in completely benign, highly differentiated lesions, such as conventional lipoma, as well as in undifferentiated, extremely aggressive tumors, like Ewing sarcoma and undifferentiated small round cell sarcomas (Table 1). Instead, one obvious explanation for the lack of gene fusions in some STT entities may be sought in the trivial fact that they have not been investigated in sufficient detail. For some tumors, like inclusion body fibromatosis or benign Triton tumor, there are simply no published genetic data at all, while for other more common, highly malignant lesions, like angiosarcoma or leiomyosarcoma, the search for potential gene fusions might have been thwarted by the typically very complex genomic rearrangements detected at chromosome banding or array-based studies (Guillou and Aurias,

2010). Although it was for a long time assumed that gene fusions were restricted to neoplasms with balanced chromosomal rearrangements, NGS-based studies of numerous malignancies with complex genomic changes have unequivocally shown that pathogenetically important gene fusions may be found also in tumor types that generally have heavily rearranged genomes (Mertens et al., 2015; Yoshihara et al., 2015). Thus, it would be highly surprising if they were not to be detected also in, e.g., angiosarcoma or leiomyosarcoma once these tumor types are subjected to large-scale transcriptome or whole-genome sequencing; support for this notion may be derived from the recent description of gene fusions in a small subset of undifferentiated pleomorphic sarcoma (Hofvander et al., 2015). Whether such gene fusions will turn out to be rare, like in lung cancer (McCoach and Doebele, 2014), or frequent, like in prostate cancer (Rubin et al., 2011), remains to be elucidated. A third explanation for the lack of gene fusions in some entities is that they may develop through other types of mutation. Indeed, for some STT types for which comprehensive data have emerged it seems as if gene fusions are rare or absent. For instance, in-depth genomic analysis of embryonal rhabdomyosarcomas has disclosed that they, in contrast to alveolar rhabdomyosarcomas, develop through characteristic combinations of point mutations and chromosomal and allelic imbalances (Shern et al., 2014), while some tumors, like desmoid-type fibromatosis or gastrointestinal stromal tumor, display near-universal mutations of a limited set of genes (Miettinen and Lasota, 2013; Crago et al., 2015).

In this context, it should be emphasized that not all gene fusions or fusion transcripts are pathogenetically relevant (Mertens et al., 2015). This could be illustrated by the three tumor types—atypical lipomatous tumor, dedifferentiated liposarcoma, and unclassified spindle cell sarcoma—in which mainly nonrecurrent gene fusions have been reported (Table 1). In all three tumor types, the gene fusions that have been reported derive from NGS studies of one or a few cases. The findings in these tumors are in line with the observation that gene fusions often are formed as a by-product of the extensive reshuffling of genetic material that is associated with gene amplification (Yoshihara et al., 2015).

ONE VERSUS MULTIPLE GENE FUSIONS IN THE SAME STT

Some of the STT subtypes with known gene fusions currently have only one highly prevalent variant, like *COL1A1-PDGFB* in dermatofibrosarcoma protuberans and giant cell fibroblastoma, *ETV6-NTRK3* in infantile fibrosarcoma, *NAB2-STAT6* in solitary fibrous tumor, or *EWSR1-WT1* in desmoplastic small round cell tumor, indicating that these particular gene combinations are crucial for tumorigenesis (Tables 1 and 2). The extreme example here would be pericytoma with t(7;12), which by definition will always have an *ACTB-GLI1* fusion (Dahlén et al., 2004). At present, however, this remains the only STT defined by its genetic features, in contrast to the current view on hematopoietic neoplasms, where genetic markers are mandatory for several diagnoses (Swerdlow et al., 2008). The lesson learnt from leukemias, which have been analyzed in far greater detail than STT, is that eventually all morphological sub-types will display some heterogeneity, either in the form of alternative gene fusions or by other types of mutation affecting the same critical pathway (Mitelman et al., 2007). In line with this, recent studies combining IHC for STAT6 expression and genetic tools for the detection of the *NAB2-STAT6* fusion strongly indicate

that there must, in rare cases, exist alternate ways of activating STAT6 expression in solitary fibrous tumor (Vogels et al., 2014; Tai et al., 2015).

Many STT are already known to display several related, recurrent as well as nonrecurrent, gene fusions, a variation that often seems to have little or no discernible impact on the morphology or biology of the tumor. For instance, there are no proved clinico-pathologic differences among lipomas with different 3′-partners to the *HMGA2* gene or between myxoid liposarcomas carrying the *FUS-DDIT3* or the *EWSR1-DDIT3* fusion (Dal Cin et al., 1997; Bartuma et al., 2007). In other STT, however, such variation does seem to be of significance. The best example is probably alveolar rhabdomyosarcoma, in which the *PAX3-FOXO1* and *PAX7-FOXO1* fusions account for some 65 and 20%, respectively, of all cases (Shern et al., 2014). While children with *PAX*-fusion positive aleolar rhabdomyosarcoma have significantly worse prognosis than those with fusion-negative tumors, patients with *PAX3-FOXO1* positive tumors have a particularly poor outcome (Missiaglia et al., 2012); in addition, the patterns of secondary changes differ between *PAX3-FOXO1* and *PAX7-FOXO1* positive cases (Shern et al., 2014). Additional examples include synovial sarcomas with *SS18-SSX1* vs. *SS18-SSX2*, where the former fusion is relatively more common in biphasic tumors (Ladanyi et al., 2002), benign fibrous histiocytoma, where *ALK* fusions seem to be restricted to the epithelioid sub-type whereas *PRKC* fusions have been detected in several subtypes (Doyle et al., 2015; Walther et al., 2015), and Ewing sarcoma/undifferentiated round cell sarcomas, where the fusion partners to *EWSR1* (*FLI1* and *ERG* vs less common Ets family genes) seem to be associated with patient age and tumor location (Wang et al., 2007). However, the data are still scarce, and it will require large collaborative efforts to clarify the clinicopathologic relevance of the gene fusion heterogeneity in STT.

In STT with multiple recurrent gene fusions, one is typically (much) more common than the other(s). It has been suggested that this bias is due to the transcriptional direction of the respective genes, i.e., gene fusions that could arise through only two DNA double strand breaks (DSB; trans-location, inversion, interstitial deletion) would be more common than those (insertion, complex rearrangements) that require more breaks. Indeed, of the recurrent gene fusions, 51 involved two genes that are transcribed in the same direction, i.e., both from the telomere towards the centromere or vice versa, while 27 involved genes that are transcribed in opposite directions (Table 2). This could then explain why, e.g., *FUS-DDIT3* is so much more common than *EWSR1-DDIT3* in myxoid liposarcoma and an *SS18-SSX3* has never been found in synovial sarcoma. However, most likely, this explanation is too simplistic because some STT have more recurrent fusions arising through complex rearrangements than from rearrangements requiring only two DNA DSB. For instance, of the 10 recurrent gene fusions in inflammatory myofibroblastic tumors, seven involve genes transcribed in opposite directions, as is the case also for all known recurrent gene fusions in SFT, sclerosing epithelioid fibrosarcoma, and ossifying fibromyxoid tumor. In some instances, as for SFT, this could be explained by the close location of the two genes, but in inflammatory myofibroblastic tumors, sclerosing epithelioid fibrosarcoma, and ossifying fibromyxoid tumor there is no obvious explanation for the abundance of gene fusions arising through complex genomic rearrangements. It could here be mentioned that the fusions arising through more complex rearrangements often are more difficult to detect by FISH, because the fusion event is typically seen on only one of the two derivate chromosomes.

OVERLAP AMONG STT AND WITH OTHER TUMORS

Regardless of its causes and consequences, the main drawback in the routine molecular work-up is related to the increasing number of gene fusions that have to be assessed in order to support or refute a diagnosis. To some extent this problem is reduced by investigating only one of the two gene partners at a time, instead of the chimeric fusion product. Thus, interphase FISH with a break-apart probe for *EWSR1*, *DDIT3* or *PLAG1* readily identifies all recurrent gene fusions in Ewing sarcoma, myxoid liposarcoma, or lipoblastoma, respectively. However, as some genes are more promiscuous, being recurrently involved in many different STT, this approach opens up for other diagnostic problems (Table 1). The most prominent example here is *EWSR1*, which is involved in gene fusions in 10 different STT, followed by *FUS* in six entities; several other genes also serve as hubs in extensive networks of gene fusions (Fig. 2). While this overlap among STT is of little clinical concern in some cases, e.g., an angiomatoid fibrous histiocytoma is not morphologically mistaken for a myxoid liposarcoma; it becomes a problem when the differential diagnoses are more similar, like desmoplastic small round cell tumor and Ewing sarcoma. This problem should be reduced once NGS-based approaches replace the currently used technologies, allowing for detailed and comprehensive detection of gene fusions (Mertens and Tayebwa, 2014).

From a biological point of view, an even more intriguing situation is when the identical gene fusion is shared by many STT, like *EWSR1-CREB1* in angiomatoid fibrous histiocytoma and clear cell sarcoma [as well as pulmonary myxoid sarcoma (Thway et al., 2011)] or *FUS-CREB3L2* in low-grade fibromyxoid sarcoma and sclerosing epithelioid fibrosarcoma (Table 2). Because there is good reason to believe that these gene fusions are strong driver mutations, the morphologic and clinical differences between the tumor types must be explained either by different sets of additional mutations and/or different cellular origins. While the effect of the mutational background of gene fusion-positive STT remains poorly investigated and thus difficult to evaluate (e.g., Robinson et al., 2013; Joseph et al., 2014; Shern et al., 2014), some experimental data suggest that the cell of origin is critical for tumor cell morphology. For instance, Straessler et al. (2013) demonstrated that conditional expression of *EWSR1-ATF1* in a mouse model resulted in slightly different tumor phenotypes depending on the cell type, and its differentiation stage, in which the fusion was expressed. Possibly, this could also explain why some fusion partners occur in several tumors, with different malignant potential, of the same line of differentiation. For instance, *FOSB* is involved in benign epithelioid hemangiomas as well as borderline malignant pseudomyogenic hemangioendotheliomas (Table 1).

As expected, many STT display the same type of fusion(s) as morphologically identical lesions arising in bone (Table 2). Thus, no less than 14 of the recurrent gene fusions that have been described in STT have also been described in primary intraskeletal tumors. More unexpectedly, and again emphasizing the importance of the cell type in which the mutation occurs, some gene fusions in STT are shared with neoplasms of other lineages, such as leukemias, lymphomas, and carcinomas. For example, some *ALK* fusions in inflammatory myofibroblastic tumor are shared with malignant lymphomas and lung cancer, and *TFE3* fusions in alveolar soft part sarcoma, PEComa, and epithelioid hemangioendothelioma are found also in kidney cancer (Table 2). The most versatile gene fusion in this context is

ETV6-NTRK3, the molecular hallmark of infantile fibrosarcoma. The same gene fusion has been identified also in acute myeloid leukemia, mesoblastic nephroma, secretory carcinoma of the breast and salivary glands, adenocarcinoma of the colon and thyroid, pediatric glioma, and Ewing sarcoma (Mitelman et al., 2015).

GENE CLASSES

Transcription Factors

While almost all known gene fusions in STT ultimately affect the transcription of multiple other genes, the mechanisms by which they do so vary. Most human genes and their encoded proteins have more than one function, depending on how, when and where they are expressed, making it difficult to classify gene fusions into distinct, separate subgroups. For instance, the EWSR1 protein is usually classified as RNA-binding, but is in addition known to interact also with other proteins as well as with DNA (Tan and Manley, 2009). Furthermore, the part contributed to the chimeric protein may lack the domain(s) used for categorizing the wild type protein, e.g., NCOA2 is formally classified as a transcription factor (TF), but the DNA-binding part of the protein is never included in the pathogenetically important fusion proteins (see below). Still, an attempt to subdivide broadly the recurrent gene fusions in STT according to type of protein affected shows that most (52/78) fusions involve a proper TF or another type of protein, such as transcriptional co-activators or corepressors, directly involved in DNA transcription (Table 3). The Human Protein Atlas (http://www.proteinatlas.org/) currently lists more than 1,500 human genes that encode TFs, which can be further subdivided into superclasses, classes, families, and subfamilies on the basis of their DNA-binding domains (Wingender et al., 2012; http://www.edgar-wingender.de/huTF_classification.html). The 41 different TF-encoding genes that are recurrently involved in gene fusions in STT belong to 7 of the 10 superclasses and to 13 of the 40 classes, with some classes and families being more commonly affected than others: six genes each encode basic leucine zipper factors (bZIP; *ATF1*, *CREB1*, *CREB3L1*, *CREB3L2*, *DDIT3*, and *FOSB*), C2H2 zinc finger factors (*C2H2*; *GLI1*, *KLF17*, *PLAG1*, *PRDM10*, *WT1*, and *ZNF444*), or tryptophan cluster factors (TCf; *ERG*, *ETV1*, *ETV4*, *ETV6*, *FEV*, and *FLI1*), and five code for basic helix-loop-helix factors (bHLH; *AHRR*, *HEY1*, *NCOA1*, *NCOA2*, and *TFE3*); notably, all six TCf belong to the family of Ets-related factors, all C2H2 except KLF17 are included in the “more than three adjacent zinc finger factors” family, and the first four bZIP belong to the family of CREB-related factors (Table 3). Thus, the repertoire of TFs involved in fusions in STT is clearly nonrandom, and the involvement of a specific TF is typically seen in only one tumor type (for exceptions, see above); for instance, only Ewing sarcoma shows recurrent fusions involving an Ets-related factor as the carboxy-terminal partner.

Why, then, are some TFs specifically associated with only some morphologies, and why are some transcription factors never involved? One explanation would be that only a limited set of TFs, and their target genes, are of relevance to the cells in which the tumors originate, i.e., only some developmental lineages are permissive for neoplastic transformation. Indeed, the few STT-associated chimeric TFs that have been analyzed in experimental systems, such as EWSR1-FLI1 or EWSR1-ATF1, show that only certain cell types can be transformed, that

different genetic programs are affected in different cell types, and that the phenotypic effects vary dependent on in which cell it is expressed (Patel et al., 2012; Straessler et al., 2013; Riggi et al., 2014). Some further support for this notion could perhaps also be derived from STT showing differentiation towards a “normal” lineage, like fat or striated muscle, as in lipoma, myxoid liposarcoma, and alveolar rhabdomyosarcoma. Studies on normal, physiological development have disclosed critical roles for HMGA2 and DDIT3 in adipogenesis (Batchvarova et al., 1995; Thies et al., 2014) and for PAX3 and PAX7 in rhabdomyogenesis (Buckingham and Relaix, 2007). Furthermore, highly recurrent gene fusions in congenital spindle cell rhabdomyosarcoma involve critical transcriptional activators of muscle-specific genes, such as *VGLL2*, *TEAD1*, and *SRF* (Alaggio et al., in press). However, many STT do not display any discernible or distinct line of differentiation. In addition, the cell of origin is unknown in most cases, making it difficult to speculate on why a specific TF is associated with a specific STT subtype. Still, it seems clear that the effect of the chimeric TF is not limited to activation or repression of genes normally regulated by the wild-type TF, and that the role of the amino-terminal partner is more complex than simply potentiating the transcription of TF target genes (Riggi et al., 2014).

TFs typically occur as carboxy-terminal partners in the fusions, where they retain their DNA-binding domain(s) in the chimeric protein. In some fusions, like those involving the Ets family of TFs, the concomitant loss of regulatory amino-terminal sequences seems to be necessary for a tumorigenic effect (Hollenhorst et al., 2011; Cooper et al., 2014), whereas in others, like DDIT3 in myxoid liposarcoma or PLAG1 in lipoblastoma, the complete coding sequence is included in the fusion. The role of the amino-terminal partner is then usually to provide a more active promoter and/or transactivating domain(s) but, as discussed above, additional effects may be achieved. In some subtypes the gene fusion involves two TFs (Tables 1 and 2). Notably, NCOA2 is the 3′-partner in several recurrent fusions with other TF-encoding genes: AHRR in angiofibroma of soft tissue, *HEY1* in mesenchymal chondrosarcoma, and *PAX3* in alveolar rhabdomyosarcoma, as well as non-recurrent ones (*GTF2I* in angiofibroma of soft tissue and *SRF* in spindle cell rhabdomyosarcoma). *NCOA2* encodes a member of the p160 steroid receptor coactivator (SRC) family and contains three structural domains: an N-terminal bHLH/PAS domain that can bind to DNA as well as heterodimerize with a variety of proteins, a central region with three LXXLL motifs that interact with nuclear hormone receptors, and a C-terminal portion with two transcriptional activation domains (Xu et al., 2009). One of them binds other coactivators, such as CREBBP and EP300, which leads to chromatin remodelling, while the other is responsible for interaction with histone methyltransferases, coactivator-associated arginine methyltransferase 1, and PRMT1 (Xu et al., 2009). In the STT-associated fusions involving NCOA2, the chimeric protein always retains the DNA-binding parts of the 5′ TF and adds the two transcriptional activation domains from NCOA2. Thus, in some subtypes the important impact on differentiation is derived from the spec-ificity of the amino-terminal TF. Similar to *NCOA2*, *CITED2* has recently been reported as a recurrent 3′ partner in congenital spindle cell rhabdomyosarcoma, preserving its CREBBP/EP300 interaction domain in the fusion protein (Alaggio et al., in press).

There is also an example of a TF serving as the amino-terminal partner to a protein kinase (PK): the ETV6-NTRK3 fusion in infantile fibrosarcoma. Here, the TF ETV6 contributes

with a SAM domain, corresponding to the PNT domain in the Est family of TF, allowing for polymerization and constitutive activation of the tyrosine kinase domain of NTRK3 (Cetinbas et al., 2013). Yet another scenario is illustrated by conventional lipoma; some 75% of these tumors have a rearrangement of the *HMGA2* gene, resulting in either an in-frame fusion transcript or in truncation of the gene, typically after the first three exons that encode the AT-hook domains (Lee and Dutta, 2007). It was shown that functional inactivation of the 3′ untranslated region of *HMGA2*, which contains multiple binding sites for the *let-7* family of microRNAs, results in upregulation of *HMGA2* by reducing *HMGA2* mRNA degradation in the cytoplasm. Functional studies of different *HMGA2* constructs have shown that the cellular consequences are the same (Fedele et al., 1998), raising questions about why some gene fusions are recurrent. In summary, TFs are involved in a variety of ways in STT.

The numerous gene fusions encoding chimeric TFs make them appealing treatment targets in STT. However, this task has been notoriously difficult, and therapeutical efforts have thus shifted toward down-stream targets of the chimeric proteins. An additional challenge in developing new drugs for STT treatment is that these tumors are rare. Thus, whenever gene fusions are shared with other, more common neoplasms, the chances of developing new, efficient drugs increase. Indeed, the high incidence of fusions involving Ets family proteins also in prostate cancer has spurred interest, and several promising studies are on-going (Cooper et al., 2014; Feng et al., 2014).

Protein Kinases

The second largest group of proteins involved in gene fusions in STT comprises PKs, all of which, except PRKCB (a serine/threonine kinase), are receptor tyrosine kinases. In all cases, the PK-encoding gene is the 3′-partner and the result of the fusion at the protein level is a constitutive activation of the kinase domain of a truncated PK (Table 3). The tumor types showing such gene fusions—notably inflammatory myofibroblastic tumor and benign fibrous histiocytoma—typically display a large variety of different 5′-partners, reflecting that the main role of the 5′-partner is to ensure a high level of transcription by providing a more active promoter, but also loss of regulatory elements from the wild-type PK may be important (Table 1). These aspects could explain why no single gene fusion makes up more than some 15% of the cases of inflammatory myofibroblastic tumor or benign fibrous histiocytoma (Table 2). The only exception at the moment—phosphaturic mesenchymal tumor, in which 60% of reported cases display a *FN1-FGFR1* fusion—can perhaps be explained by the limited number of cases ($n = 15$) that has been reported. In addition to providing an active promoter, the amino-terminal partner may be important also through contributing oligomerization domains or by ensuring a particular subcellular localization of the chimeric protein. An indication that the involvement of a particular PK is less tissue-specific than for TFs could be gleaned from the fact that several of the STT-associated gene fusions are seen in many other types of neoplasia, *ETV6-NTRK3* and *EML4-ALK* constituting the most prominent examples (Table 2). Furthermore, the PK that is most often involved in STT-associated chimeras—ALK—is activated by numerous other fusions, as well as other types of mutation, in a large number of neoplasms (Mariño-Enriquez and Dal Cin, 2013; Mitelman et al., 2015).

Another feature shared by inflammatory myofibroblastic tumor and benign fibrous histiocytoma is that the type of PK involved in the fusions varies, i.e., either ALK, ROS1, or PDGFRB in the former and either ALK or protein kinase C in the latter. As mentioned above, this variation correlates with morphological subtype in benign fibrous histiocytoma; whether clinicopathological differences caused by type of PK fusion exist also among inflammatory myofibroblastic tumor remains to be seen. For obvious reasons, this tumor type is the STT subtype with PK-encoding gene fusions that has attracted most clinical attention. While benign fibrous histiocytoma and phospathaturic mesenchymal tumor are considered benign and metastases only rarely develop in infantile fibrosarcoma, inflammatory myofibroblastic tumor is more aggressive (Fletcher et al., 2013). Thus, the chimeric PKs here, as in other malignancies with receptor tyrosine kinases activated by gene fusions/mutations, offer an excellent therapeutic target (Shaw et al., 2013; Lovly et al., 2014 Stransky et al., 2014).

Chromatin Regulators

Proteins that are involved in chromatin modification and remodeling have emerged as important players in tumorigenesis (Chen and Dent, 2014). Gene fusions resulting in distorted chromatin regulation have been recognized in leukemias for two decades, with fusions involving the *KMT2A* (previously known as *MLL*) gene as a well-known example (Krivtsov and Armstrong, 2007). As expected, the cellular effects of such fusion proteins are more global than for fusions involving TFs with their specific sets of target genes. Thus, STT with gene fusions affecting chromatin regulation are either undifferentiated, as exemplified by undifferentiated round cell sarcomas with the *BCOR-CCNB3* fusion, or display disparate lines of differentiation, such as synovial sarcoma with *SS18-SSX* fusions or ossifying fibromyxoid tumor with PHF1 fusions.

Most likely, the significance of chromatin remodeling extends far beyond what is suggested by the crude classification in Table 3; several of the fusions listed among TFs probably to some extent exert their pathogenetic impact by also affecting the chromatin configuration. For instance, the part of the NAB2 protein that replaces the carboxy-terminal part of STAT6 in the NAB2-STAT6 fusion in solitary fibrous tumor is known to interact with the NuRD complex. Furthermore, in all the fusions combining an amino-terminal TF with the carboxy-terminal part of NCOA1 or NCOA2, the histone methyltransferase-interacting domains of the NCOA proteins will be included, and also the EWSR1-FLI1 chimera can alter chromatin (Patel et al., 2012). There is thus reason to hope that drugs, such as DNA methylation and his-tone deacetylase inhibitors, that were developed for other neoplasms might be useful for epigenetic treatment of many malignant STT, too (Højfeldt et al., 2013).

Altered Growth Factor Signaling and Other Mechanisms

At first glance, a few fusions in STT seem to affect neither TFs, PKs, nor chromatin modifiers (Table 3). Indirectly, however, their effect is similar to what has been described above. Two gene fusions involve growth factors—the *COL1A1-PDGFB* fusion in dermatofibrosarcoma protuberans/giant cell fibroblastoma and the *COL6A3-CSF1* fusion in tenosyno-vial giant cell tumor—that result in constitutive activation of their respective tyrosine kinase receptors, PDGFRB and CSF1R. Hence, in line with targeted therapies for

fusions involving PKs, the use of a tyrosine kinase inhibitor, such as Imatinib, is of clinical value in unresectable or metastatic cases of dermatofibrosarcoma protuberans (Mentzel et al., 2013). Also activated CSF1R, which belongs to the same family of tyrosine kinases as PDGFRB, should respond to treatment with tyrosine kinase inhibitors, but the benefits of pharmacological treatment of tenosynovial giant cell tumors are less obvious (Cassier et al., 2012). *USP6*, which is activated through promoter-swapping with *MYH9* in some 75% of cases of nodular fasciitis (Table 2), encodes an ubiquitin-specific protease. Similar *USP6* fusions have been described also in primary aneurysmal bone cyst and in giant cell reparative granuloma of the hands and feet, but with other or unknown 5′-partners (Oliveira et al., 2004; Agaram et al., 2014). In all cases, it seems as if the contribution of the 5′-partner is restricted to providing enhanced transcription of *USP6*. Preliminary data suggest that overex-pressed USP6 results in activation of the NF-κB TF complex, but the exact mechanisms remain to be elucidated. If also malignant STT, as has been shown for other types of malignancy (Mitelman et al., 2015), turn out to display fusions activating ubiquitin-specific proteases, promising treatment options have emerged (Pal et al., 2014).

An exception to the rule that recurrent fusion proteins in STT affect the transcription of other genes was recently provided by Stransky et al. (2014), who identified a TRIO-TERT chimera in two dedifferentiated liposarcomas. STT typically maintain telomere length through mutations in the promoter region of the *TERT* gene (Killela et al., 2013) or by alternative lengthening of telomeres (Taylor et al., 2011). The fusion described by Stransky et al. (2014), which involved the nonenzymatic part of the PK TRIO, resulted in highly increased expression of the *TERT* gene, and thus represents a novel mechanism to ensure the telomere integrity of STT cells. Another intriguing mechanism is exemplified by glomus tumors, in which *MIR143-NOTCH* fusions have been detected in both benign and malignant lesions (Mosquera et al., 2013). Most likely, the strong promoter of *MIR143* drives the expression of the NOTCH intracellular domain, which translocates to the nucleus and induces the transcriptional program associated with NOTCH activation. Thus, such tumors might potentially be sensitive to targeting with γ-secretase inhibitors.

CONCLUSIONS

As the NGS technologies continue to improve technically and to become cheaper and more user-friendly, they will gradually replace old-fashioned methods for detecting gene fusions not only in research projects but also in the clinical setting. Hence, the number of known gene fusions in STT can within the next few years be expected to show the same dramatic increase as has been witnessed for carcinomas (Mertens et al., 2015). Because probably only a few of them will be path-ogenetically relevant, the sorting out of driver mutations from passenger mutations will be an arduous task, hopefully facilitated by the development of more sophisticated algorithms for data analysis (Yoshihara et al., 2015). Much also remains to be done when it comes to elucidating the pathogenetic mechanisms involved, the interaction between gene fusions and other mutations, and the cellular contexts in which they arise. An important step in this endeavour is the creation of transgenic mouse models, which so far exist for only four gene fusions (*EWSR1-ATF1*, *FUS-DDIT3*, *PAX3-FOXO1*, and *SS18-SSX2*) and truncated *HMGA2*; all of these models develop the corresponding human tumors (Arlotta et al., 2000; Pérez-Losada et al., 2000; Keller et al., 2004; Haldar et

al., 2007; Straessler et al., 2013). Most importantly, however, the new data need to be evaluated with regard to clinical significance, i.e., their diagnostic impact and their usefulness for treatment stratification and targeted therapy will have to be established. That gene fusion status is already of seminal importance for the management of cancer patients, such as chronic myeloid leukemia with *BCR-ABL1* or lung cancer with *ALK* fusions, is well known but, as recently shown for inflammatory myofibroblastic tumor (Lovly et al., 2014), many new actionable targets are likely to be identified also in malignant STT for which currently no cure is available unless presenting as a localized disease.

ACKNOWLEDGMENT

The authors are indebted to Prof. Göran Stenman for critical reading of the manuscript.

Supported by: The Swedish Cancer Society, the Gunnar Nilsson Cancer Foundation, the IngaBritt and Arne Lundberg Foundation, the Swedish Childhood Cancer Foundation, the Medical Faculty of Lund University, and Governmental Funding of Clinical Research within the National Health Service.

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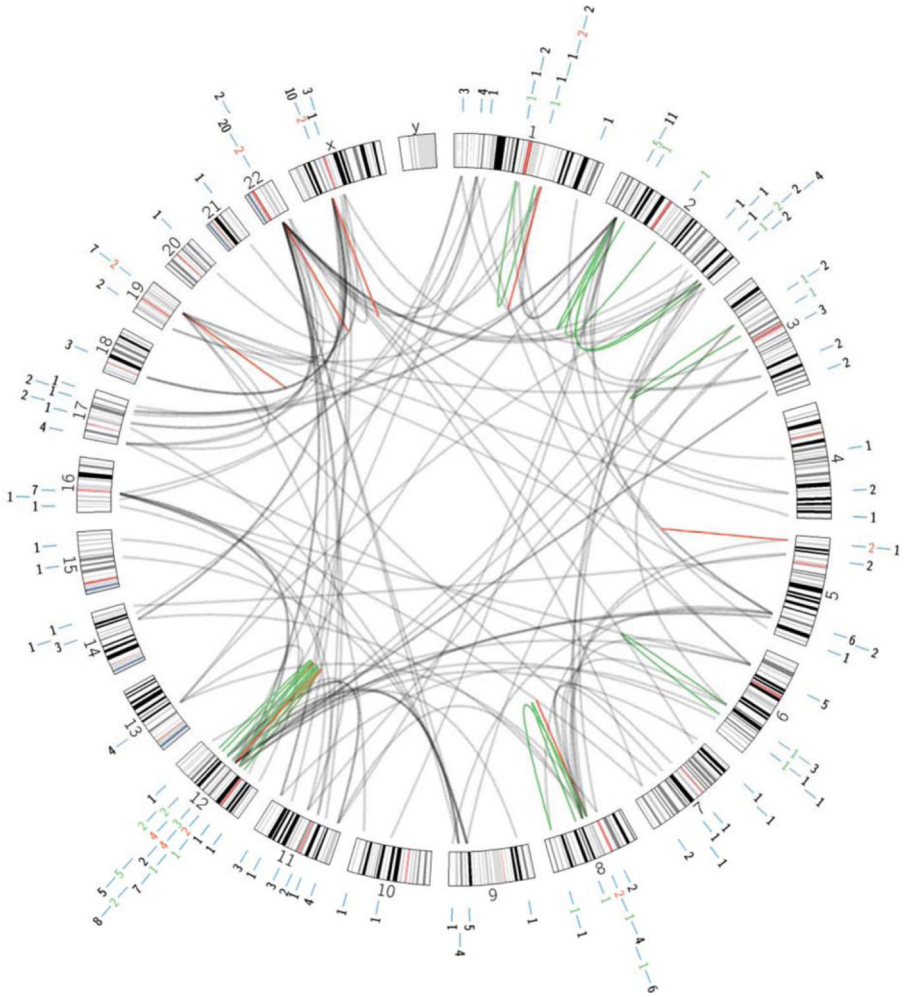

Figure 1.

Circos plot showing the chromosomal distribution of genes involved in recurrent and non-recurrent gene fusiosn in soft tissue tumors. Black lines 5 fusions involving genes on different chromosomes; green lines 5 fusions arising through intra-chromosomal rearrangements; red lines 5 fusion of genes located in the same chromosome band. The numbers outside the circos plot refer to the number of different gene fusions per chromosome band. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

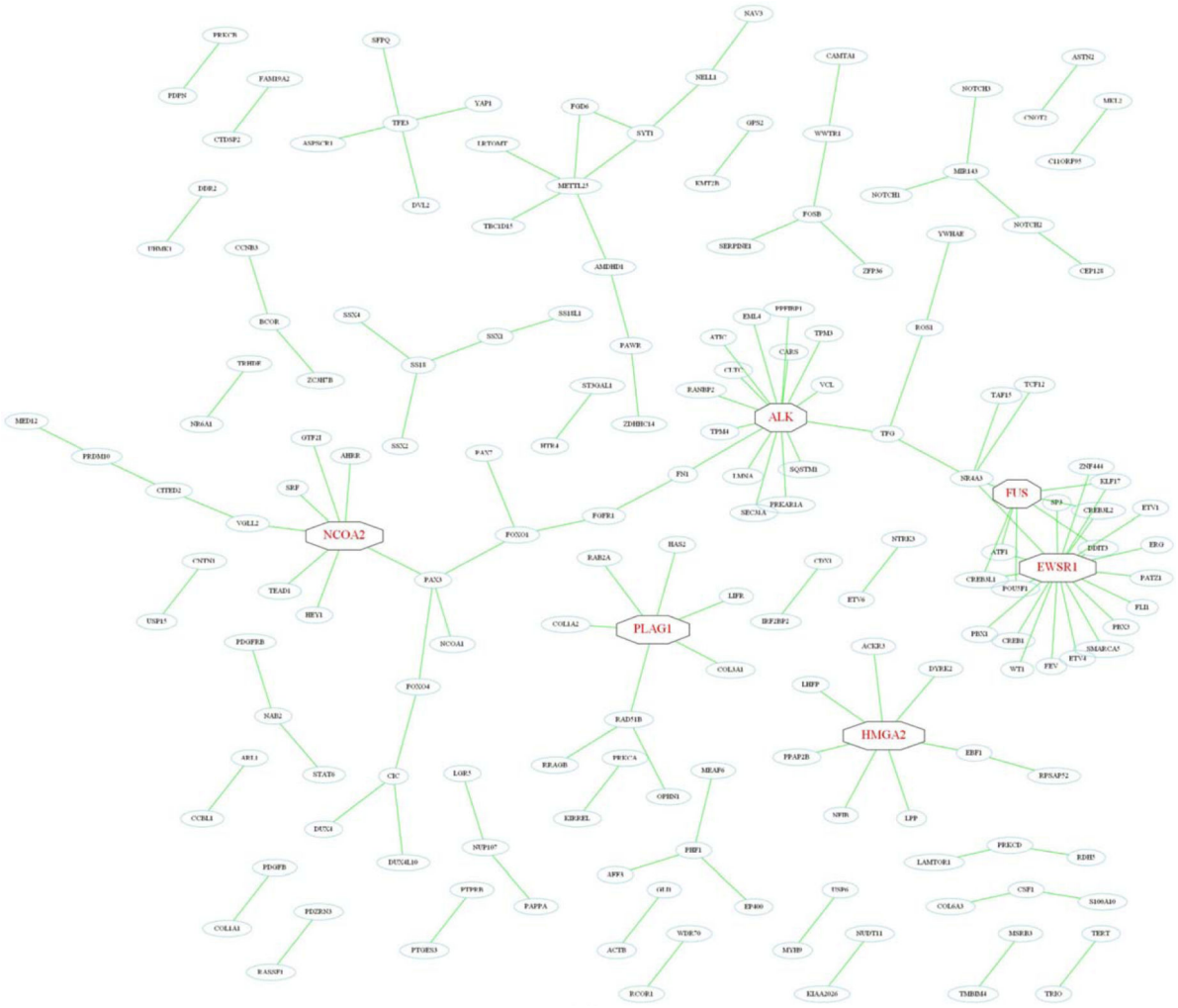

Figure 2.

Network of gene fusions in soft tissue tumors. Some genes—*ALK*, *EWSR1*, *FUS*, *HMGA2*, *NCOA2*, and *PLAG1* (indicated in red)—are promiscuous in the sense that they recombine with more than five different partners, leading to the formation of interconnected networks. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 1

Gene Fusions in Soft Tissue Tumors[a]

Tumor	Recurrent fusion[b]	Single case
Adipocyte tumors		
Lipoma	*EBF1-RPSAP52*	*HMGA2-EBF1*
	HMGA2-ACKR3	*HMGA2-LHFP*
	HMGA2-LPP	*LPP-C12orf9*
	HMGA2-NFIB	
	HMGA2-PPAP2B	
Lipoblastoma	*COL1A2-PLAG1*	*RAB2A-PLAG1*
	COL3A1-PLAG1	*RAD51B-PLAG1*
	HAS2-PLAG1	
Chondroid lipoma	***C11orf95-MKL2***	
Myxoid/round cell liposarcoma	***FUS-DDIT3***	
	EWSR1-DDIT3	
Atypical lipomatous tumor		*METTL25-AMDHD1*[c]
		METTL25-FGD6[c]
		LRTOMT-METTL25[c]
		NELL1-NAV3[c]
		NELL1-SYT1[c]
		PAWR-AMDHD1[c]
		SYT1-METTL25[c]
		SYT1-FGD6[c]
		TBC1D15-METTL25[c]
		UHMK1-DDR2[c]
		ZDHHC14-PAWR[c]
Dedifferentiated liposarcoma	*TRIO-TERT*	*CNOT2-ASTN2*
		CTDSP2-FAM19A2
		NR6A1-TRHDE
		NUP107-LGR5
		NUP107-PAPPA
		RCOR1-WDR70
Fibroblastic/Myofibroblastic tumors		
Nodular fasciitis	***MYH9-USP6***	
Soft tissue angiofibroma	***AHRR-NCOA2***	*GTF2I-NCOA2*
Dermatofibrosarcoma protuberans[d]	***COL1A1-PDGFB***	
Solitary fibrous tumor	***NAB2-STAT6***	
Infantile fibrosarcoma	***ETV6-NTRK3***	

Tumor	Recurrent fusion[b]	Single case
Low-grade fibromyxoid sarcoma	*EWSR1-CREB3L1*	
	FUS-CREB3L1	
	FUS-CREB3L2	
Sclerosing epithelioid fibrosarcoma	***EWSR1-CREB3L1***	
	EWSR1-CREB3L2	
	FUS-CREB3L2	
Inflammatory myofibroblastic tumor	*CARS-ALK*	*ATIC-ALK*
	CLTC-ALK	*LMNA-ALK*
	EML4-ALK	*NAB2-PDGFRB*
	FN1-ALK	*PRKAR1A-ALK*
	PPFIBP1-ALK	*TFG-ALK*
	RANBP2-ALK	*YWHAE-ROS1*
	SEC31A-ALK	
	TFG-ROS1	
	TPM3-ALK	
	TPM4-ALK	
So-called fibrohistiocytic tumors		
Tenosynovial giant cell tumor	***COL6A3-CSF1***	*CSF1-S100A10*
Benign fibrous histiocytoma	*PDPN-PRKCB*	*KIRREL-PRKCA*
		LAMTOR1-PRKCD
		RDH5-PRKCD
		SQSTM1-ALK
		VCL-ALK
Pericytic (perivascular) tumors		
Glomus tumor	***MIR143-NOTCH2***	*MIR143-NOTCH1*
		MIR143-NOTCH3
		NOTCH2-CEP128
Pericytoma with t(7;l2)	***ACTB-GLI1***	
Skeletal muscle tumors		
Alveolar rhabdomyosarcoma	***PAX3-FOXO1***	*FOXO1-FGFR1*
	PAX3-NCOA1	*PAX3-FOXO4*
	PAX3-NCOA2	
	PAX7-FOXO1	
Congenital spindle cell rhabdomyosarcoma	*TEAD1-NCOA2*	*SRF-NCOA2*
	VGLL2-CITED2	
	VGLL2-NCOA2	
Vascular tumors		
Epithelioid hemangioma	***ZFP36-FOSB***	*WWTR1-FOSB*
Pseudomyogenic hemangioendothelioma	***SERPINE1-FOSB***	
Epithelioid hemangioendothelioma	***WWTR1-CAMTA1***	
	YAP1-TFE3	
Tumors of uncertain differentiation		

Tumor	Recurrent fusion[b]	Single case
Angiomatoid fibrous histiocytoma	***EWSR1-CREB1***	
	FUS-ATF1	
	EWSR1-ATF1	
Biphenotypic sinonasal sarcoma	***PAX3-MAML3***	*PAX3-FOXO1*
	PAX3-NCOA1	
Ossifying fibromyxoid tumor	***EP400-PHF1***	*ZC3H7B-BCOR*
	MEAF6-PHF1	
Myoepithelioma/mixed tumor	*EWSR1-PBX1*	*EWSR1-ATF1*
	EWSR1-POU5F1	*EWSR1-KLF17*
	EWSR1-ZNF444	*EWSR1-PBX3*
	FUS-KLF17	*LIFR-PLAG1*
Phosphaturic mesenchymal tumor	***FN1-FGFR1***	
Synovial sarcoma	***SS18-SSX1***	*SS18L1-SSX1*
	SS18-SSX2	
	SS18-SSX4	
Alveolar soft part sarcoma	***ASPSCR1-TFE3***	
Clear cell sarcoma	***EWSR1-CREB1***	
	EWSR1-ATF1	
Extraskeletal myxoid chondrosarcoma	***EWSR1-NR4A3***	*FUS-NR4A3*
	TAF15-NR4A3	*TCF12-NR4A3*
		TFG-NR4A3
Desmoplastic small round cell tumor	***EWSR1-WT1***	*EWSR1-ERG*
PEComa	*RAD51B-OPHN1*	*DVL2-TFE3*
	RAD51B-RRAGB	*HTR4-ST3GAL1*
	SFPQ-TFE3	*RASSF1-PDZRN3*
Ewing sarcoma and undifferentiated/ unclassified sarcomas		
Ewing sarcoma	*EWSR1-ERG*	*EWSR1-PATZ1*
	EWSR1-ETV1	*EWSR1-SMARCA5*
	EWSR1-ETV4	
	EWSR1-FEV	
	EWSR1-FLI1	
Undifferentiated/unclassified sarcomas	***BCOR-CCNB3***	*CITED2-PRDM10*
	CIC-DUX4	*EWSR1-POU5F1*
	CIC-DUX4L10	*EWSR1-SP3*
	CIC-FOXO4	*KMT2B-GPS2*
	MED12-PRDM10	
Spindle cell sarcoma		*HMGA2-DYRK2*[c]
		PTGES3-PTPRB[c]
		TMBIM4-MSRB3[c]
		USP15-CNTN1[c]

Tumor	Recurrent fusion[b]	Single case
Chondro-osseous tumors		
Soft tissue chondroma		*HMGA2-LPP*
Mesenchymal chondrosarcoma	***HEY1-NCOA2***	*IRF2BP2-CDX1*

[a]Gene fusions were retrieved from Mitelman F, Johansson B, Mertens F (Eds.). Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer, http://cgap.nci.nih.gov/Chromosomes/Mitelman. Queried on September 24, 2015. Gene fusions occurring in the same morphologic entity but originating in bone are not included.

[b]Recurrent gene fusions have been reported in at least two cases of the same morphology. Gene fusions in bold are present in at least 10% of the tumors.

[c]These fusion genes were all detected in the same case of atypical lipomatous tumor and spindle cell sarcoma, respectively, both displaying extensive gene amplification.

[d]Includes giant cell fibroblastoma.

TABLE 2

Recurrent Gene Fusions in Soft Tissue Tumors[a]

Gene fusion	Tumor type[b]	Other tumors[c]	First described in STT
ACTB-GLI1	Pericytoma with t(7;12) (100%)	Bone	Dahleen et al., 2004
AHRR-NCOA2	Soft tissue angiofibroma (>50%)		Jin et al., 2012
ASPSCR1-TFE3	Alveolar soft part sarcoma (100%)	KC	Ladanyi et al., 2001
BCOR-CCNB3	URCS (>20%)	Bone	Pierron et al., 2012
C11ORF95-MKL2	Chondroid lipoma (>90%)		Huang et al., 2010
CARS-ALK	Inflammatory myofibroblastic tumor		Cools et al., 2002
CIC-DUX4	URCS (>25%)		Kawamura-Saito et al., 2006
CIC-DUX4L10	URCS (>25%)		Italiano et al., 2012
CIC-FOXO4	URCS	Bone	Brohl et al., 2014; Sugita et al., 2014
CLTC-ALK	Inflammatory myofibroblastic tumor (15%)	ML	Bridge et al., 2001
COL1A1-PDGFB	Dermatofibrosarcoma protuberans[b] (>95%)		Simon et al., 1997
COL1A2-PLAG1	Lipoblastoma		Hibbard et al., 2000
COL3A1-PLAG1	Lipoblastoma (>10%)		Yoshida et al., 2014
COL6A3-CSF1	Tenosynovial giant cell tumor (30%)		West et al., 2006
EBF1-RPSAP52	Lipoma		Nilsson et al., 2006
EML4-ALK	Inflammatory myofibroblastic tumor (10%)	AL, BC,CC, LC, ML, TC	Lovly et al., 2014
EP400-PHF1	Ossifying fibromyxoid tumor (45%)		Gebre-Medhin et al., 2012
ETV6-NTRK3	Infantile fibrosarcoma (>90%)	AC, AL, BC, ES, ML, MN, SGC	Knezevich et al., 1998; Rubin et al., 1998
EWSR1-ATF1	Clear cell sarcoma (>90%)	SGC, URCS,	Zucman et al., 1993a
	Angiomatoid fibrous histiocytoma	Bone, MET	Hansén Hallor et al., 2005
EWSR1-CREB1	Clear cell sarcoma (>50%)	PMS	Antonescu et al., 2006
	Angiomatoid fibrous histiocytoma (>80%)		Antonescu et al., 2007; Rossi et al., 2007
EWSR1-CREB3L1	Low-grade fibromyxoid sarcoma	URCSB	Lau et al., 2013
	Sclerosing epithelioid fibrosarcoma (>60%)		Arbajian et al., 2014; Stockman et al., 2014
EWSR1-CREB3L2	Sclerosing epithelioid fibrosarcoma (>10%)		Prieto-Granada et al., 2015; Puls et al., in press
EWSR1-DD1T3	Myxoid liposarcoma		Panagopoulos et al., 1996
EWSR1-ERG	Ewing sarcoma	URCSB, DSCRT	Zucman et al., 1993b
EWSR1-ETV1	Ewing sarcoma	Bone	Jeon et al., 1995
EWSR1-ETV4	Ewing sarcoma		Kaneko et al., 1996; Urano et al., 1996
EWSR1-FEV	Ewing sarcoma	Bone	Peter et al., 1997
EWSR1-FLI1	Ewing sarcoma (90%)	Bone	Delattre et al., 1992
EWSR1-NR4A3	ESMCS (70%)		Labelle et al., 1995
EWSR1-PBX1	Myoepithelial tumor	Bone	Brandal et al., 2008
EWSR1-POU5F1	Myoepithelial tumor	HS, SGC, URCS, URCSB	Antonescu et al., 2010
EWSR1-WT1	DSCRT (>95%)		Ladanyi and Gerald, 1994
EWSR1-ZNF444	Myoepithelial tumor		Brandal et al., 2009
FN1-ALK	Inflammatory myofibroblastic tumor		Ouchi et al., 2015

Gene fusion	Tumor type[b]	Other tumors[c]	First described in STT
FN1-FGFR1	PMT (60%)		Lee et al., 2015
FUS-ATF1	Angiomatoid fibrous histiocytoma		Waters et al., 2000
FUS-CREB3L1	Low-grade fibromyxoid sarcoma		Mertens et al., 2005
FUS-CREB3L2	Low-grade fibromyxoid sarcoma (90%)		Storlazzi et al., 2003
	Sclerosing epithelioid fibrosarcoma		Guillou et al., 2007
FUS-DDIT3	Myxoid liposarcoma (95%)		Crozat et al., 1993; Rabbitts et al., 1993
FUS-KLF17	Myoepithelial tumor	Bone	Huang et al., 2015
HAS2-PLAG1	Lipoblastoma (>10%)		Hibbard et al., 2000
HEY1-NCOA2	Mesenchymal chondrosarcoma (65%)		Nyquist et al., 2012; Wang et al., 2012
HMGA2-ACKR3	Lipoma		Broberg et al., 2002
HMGA2-LPP	Lipoma (15%)	CHL	Schoenmakers et al., 1995
HMGA2-NFIB	Lipoma	SGA	Nilsson et al., 2005
HMGA2-PPAP2B	Lipoma		Bianchini et al., 2013
MEAF6-PHF1	Ossifying fibromyxoid tumor	ESS	Antonescu et al., 2014b
MED12-PRDM10	UPS		Hofvander et al., 2015
MIR143-NOTCH2	Glomus tumor (35%)		Mosquera et al., 2013
MYH9-USP6	Nodular fasciitis (75%)		Erickson-Johnson et al., 2011
NAB2-STAT6	Solitary fibrous tumor (>95%)		Chmielecki et al., 2013; Mohajeri et al., 2013; Robinson et al., 2013
PAX3-FOXO1	Alveolar RMS (65%)		Galili et al., 1993; Shapiro et al., 1993
PAX3-MAML3	Biphenotypic sinonasal sarcoma (80%)		Wang et al., 2014
PAX3-NCOA1	Alveolar RMS		Wachtel et al., 2004
	Biphenotypic sinonasal sarcoma		Huang et al., in press
PAX3-NCOA2	Alveolar RMS		Sumegi et al., 2010
PAX7-FOXO1	Alveolar RMS (20%)		Davis et al., 1994
PDPN-PRKCB	Benign fibrous histiocytoma		Plaszczyca et al., 2014
PPFIBP1-ALK	Inflammatory myofibroblastic tumor		Takeuchi et al., 2011
RAD51B-OPHN1	PEComa		Agaram et al., 2015
RAD51B-RRAGB	PEComa		Agaram et al., 2015
RANBP2-ALK	Inflammatory myofibroblastic tumor	AL, MDS, ML	Ma et al., 2003
SEC31A-ALK	Inflammatory myofibroblastic tumor	ML	Panagopoulos et al., 2006
SERPINE1-FOSB	PMy hemangioendothelioma (100%)	Bone	Walther et al., 2014
SFPQ-TFE3	PEComa	KC	Tanaka et al., 2009
SS18-SSX1	Synovial sarcoma (60%)		Clark et al., 1994; Crew et al., 1995; de Leeuw et al., 1995
SS18-SSX2	Synovial sarcoma (35%)		Clark et al., 1994; Crew et al., 1995; de Leeuw et al., 1995
SS18-SSX4	Synovial sarcoma		Skytting et al., 1999
TAF15-NR4A3	ESMCS (25%)		Attwool et al., 1999; Panagopoulos et al., 1999; Sjögren et al., 1999
TEAD1-NCOA2	Congenital spindle cell RMS (20%)		Mosquera et al., 2013
TFG-ROS1	Inflammatory myofibroblastic tumor		Lovly et al., 2014

Gene fusion	Tumor type[b]	Other tumors[c]	First described in STT
TPM3-ALK	Inflammatory myofibroblastic tumor (15%)	ML	Lawrence et al., 2000
TPM4-ALK	Inflammatory myofibroblastic tumor	ML	Lawrence et al., 2000
TRIO-TERT	Dedifferentiated liposarcoma		Stransky et al., 2014
VGLL2-CITED2	Congenital spindle cell RMS (30%)		Alaggio et al., in press
VGLL2-NCOA2	Congenital spindle cell RMS (20%)		Alaggio et al., in press
WWTR1-CAMTA1	Epithelioid hemangioendothelioma (90%)		Errani et al., 2011; Tanas et al., 2011
YAP1-TFE3	Epithelioid hemangioendothelioma		Antonescu et al., 2013
ZFP36-FOSB	Epithelioid hemangioma (15%)	Bone	Antonescu et al., 2014a

[a]Only gene fusions that have been detected in multiple cases of a tumor type included in the WHO classification of soft tissue and bone tumors (Fletcher et al., 2013) are included; also angiofibroma of soft tissue, pericytoma with t(7;12), and biphenotypic sinonasal sarcoma were included. When a gene fusion is present in at least 10% of a specific tumor type, the approximate frequency (as suggested by cytogenetic, molecular, and/or FISH studies) is given in parentheses. Fusions between genes transcribed in the same direction, i.e., both are transcribed from the centromere towards the telomere or vice versa, are in green; fusions of genes transcribed in opposite directions are in red.

[b]DSCRT, desmoplastic small round cell tumor; ESMCS, extraskeletal myxoid chondrosarcoma; PEComa, perivascular epithelioid-cell tumor; PMT, phosphaturic mesenchymal tumor; PMy, pseudomyogenic; UPS, undifferentiated pleomorphic sarcoma; URCS, undifferentiated round cell sarcoma.

[c]Tumor(s) with same morphology and same gene fusion also described in: AC, astrocytoma; AL, acute leukemia; BC, breast carcinoma; Bone, primary skeletal lesion; CC, colon carcinoma; CHL, chondroid hamartoma of the lung; DSCRT, desmoplastic small round cell tumor; ES, Ewing sarcoma; ESS, endometrial stromal cell sarcoma of the uterus; HS, hidradenoma of the skin; KC, kidney carcinoma; LC, lung carcinoma; MDS, myelodysplastic syndrome; MET, myoepithelial tumor; ML, malignant lymphoma; MN, mesoblastic nephroma; PMS, pulmonary myxoid sarcoma; RMS, rhabdomyosarcoma; SGA, salivary gland adenoma; SGC, salivary gland carcinoma; TC, thyroid carcinoma; URCS, undifferentiated round cell sarcoma; URCSB, URCS of bone.

TABLE 3

Type of Gene Involved in Recurrent Gene Fusions in Soft Tissue Tumors[a]

Type of gene	5′ gene(s)	3′ gene(s)
Transcription factor[b]	*ACTB*	***GLI1*** (C2H2)
	AHRR (bHLH)	***NCOA2*** (bHLH)
	ASPSCR1	***TFE3*** (bHLH)
	C11orf95	***MKL2*** (TR)
	CIC (HMGf)	***DUX4*** (HDf), ***DUX4L10*** (HDf), ***FOXO4*** (F/Wf)
	COL1A2	***PLAG1*** (C2H2)
	COL3A1	***PLAG1*** (C2H2)
	EBF1 (RHRf)	*RPSAP52*
	EWSR1	***ATF1*** (bZIP), ***CREB1*** (bZIP), ***CREB3L1*** (bZIP), ***CREB3L2*** (bZIP), ***DDIT3*** (bZIP), ***ERG*** (TCf), ***ETV1*** (TCf), ***ETV4*** (TCf), ***FEV*** (TCf), ***FLI1*** (TCf), ***NR4A3*** (nrC4), ***PBX1*** (HDf), ***POU5F1*** (HDf), ***WT1*** (C2H2), ***ZNF444*** (C2H2)
	FUS	***ATF1*** (bZIP), ***CREB3L1*** (bZIP), ***CREB3L2*** (bZIP), ***DDIT3*** (bZIP), ***KLF17*** (C2H2)
	HAS2	***PLAG1*** (C2H2)
	HEY1 (bHLH)	***NCOA2*** (bHLH)
	HMGA2 (ATHf)	*ACKR3*, *LPP*, *NFIB*, *PPAP2B*
	MED12	***PRDM10*** (C2H2)
	NAB2	***STAT6*** (SDf)
	PAX3 (PBf)	***FOXO1*** (F/Wf), ***MAML3*** (TR), ***NCOA1*** (bHLH), ***NCOA2*** (bHLH)
	PAX7 (PBf)	***FOXO1*** (F/Wf)
	SERPINE1	***FOSB*** (bZIP)
	SFPQ (nOdf)	***TFE3*** (bHLH)
	TAF15	***NR4A3*** (nrC4)
	TEAD1	***NCOA2*** (bHLH)
	VGLL2	***CITED2*** (TR), ***NCOA2*** (bHLH)
	WWTR1	***CAMTA1*** (TR)
	YAP1	***TFE3*** (bHLH)
	ZFP36	***FOSB*** (bZIP)
Protein kinase	*CARS*	***ALK***
	CLTC	***ALK***
	EML4	***ALK***
	ETV6 (TCf)	***NTRK3***
	FN1	***ALK***, ***FGFR1***
	PDPN	***PRKCB***
	PPFIBP1	***ALK***
	RANBP2	***ALK***
	SEC31A	***ALK***
	TFG	***ROS1***
	TPM3	***ALK***
	TPM4	***ALK***
Chromatin regulator	***BCOR***	*CCNB3*
	EP400	***PHF1***
	MEAF6	***PHF1***
	SS18	*SSX1*, *SSX2*, *SSX4*
Growth factor	*COL1A1*	***PDGFB***
	COL6A3	***CSF1***
Other	*MIR143*	*NOTCH2*
	MYH9	*USP6*
	RAD51B	*OPHN1*, *RRAGB*
	TRIO	*TERT*

[a]Only gene fusions that are recurrent are included. Genes encoding transcription factors are high-lighted in blue, protein kinases in red, chromatin regulators in green, and growth factors in purple.

[b]Transcription factors (TFs) are further specified according to class (Wingender et al., 2012; http://tfclass.bioinf.med.uni-goettingen.de/). Also some genes that are not formally classified as TFs, but have a direct role in transcriptional regulation, are included here. ATHf, AT hook factor; bHLH, basic helix-loop-helix factor; C2H2, C2H2 zinc finger factor; F/Wf, fork head/winged helix factor; HDf, homeo domain factor; HMGf, high mobility group domain factor; nOdf, nonO domain factor; nrC4, nuclear receptor with C4 zinc fingers; PBf, paired box factor; RHRf, Rel homology region factor; SDf, STAT domain factor; TCf, tryptophan cluster factor; TR, not a formal TF, but involved in transcriptional regulation as co-activator or co-repressor.