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Novel *SS18-NEDD4* gene fusion in a primary renal synovial sarcoma

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Abstract

We report a primary renal synovial sarcoma with a novel gene fusion and unusual morphology. The patient was a 35-year-old female who was found to have a 5 cm hypocellular, myxoid spindle cell renal neoplasm that subtly permeated amongst native renal tubules. The tumor cells showed elongated hyperchromatic nuclei with ill-defined pale cytoplasm, lacking significant mitotic activity or necrosis. Based on its deceptively bland morphology, the differential diagnosis included mainly benign entities, such as metanephric stromal tumor, mixed epithelial stromal tumor (MEST), and myxoid peripheral nerve sheath tumors. A definitive diagnosis of synovial sarcoma was made only subsequently to RNA-sequencing, which revealed a novel *SS18-NEDD4* gene fusion. These results were further confirmed by fluorescence in situ hybridization using custom design break-apart probes for both genes. This case illustrates the utility of targeted RNA-sequencing in the classification of challenging tumors with deceptive morphology and identification of novel gene fusion variants. Apart from the canonical *SS18-SSX* fusion, this is only the second alternative gene fusion variant described in synovial sarcoma to date, in addition to two cases harboring the *SS18L1-SSX1* fusion.

Keywords

synovial sarcoma; renal; SS18; NEDD4; fusion

INTRODUCTION

Synovial sarcoma accounts for approximately 15% of soft tissue sarcomas in young adults[1]. The median age at diagnosis is 35 years, though the range is wide (5-85 years). Synovial

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sarcoma typically occurs in the extremities, but genetically confirmed primary synovial sarcomas have been reported in virtually every visceral organ (including lung, pleura, prostate, heart, etc.). Synovial sarcomas may recur early or late, and the 10-year survival rate is approximately 50%[1]. Renal SS have been well documented but are often challenging due to their broad differential diagnosis[2].

Synovial sarcoma is characterized by a recurrent t(X;18)(p11;q11) translocation, resulting in an in-frame fusion of all but the C-terminal 8 amino acids of the *SS18* gene (formerly *SYT*) at 18q11 with one of several genes located at the Xp11 locus, typically *SSX1* or *SSX2*, but rarely *SSX4*[3–6]. These fusions are found in >95% of confirmed synovial sarcomas. *SS18* encodes a transcriptional coactivator, while the C-terminal portions of *SSX* retained in the fusions have repressive functions; therefore, the fusion protein is thought to have both transcriptional activating and repressive functions despite lacking a DNA binding domain[3]. The *SS18-SSX* fusion proteins become part of the SWI/SNF chromatin complex, affecting chromatin remodeling and thereby dramatically impacting transcription globally, while additional epigenetic transcriptional regulation has also been demonstrated[7].

While most cases thought to represent *SS18-SSX* fusion-negative synovial sarcomas are in fact morphologic mimics (such as malignant peripheral nerve sheath tumors, cellular solitary fibrous tumors, or *BCOR-CCNB3*-fusion positive sarcomas), rare cases likely represent true synovial sarcomas with unrecognized variant fusions. At this writing, only one other synovial sarcoma variant gene fusion has been reported: an *SS18L1-SSX1* fusion resulting from a t(X;20)(p11;q13)[8,9].

We report herein a novel gene fusion in synovial sarcoma between *SS18* and the *NEDD4* gene at chromosome 15q21, identified by RNA sequencing and confirmed by fluorescence in situ hybridization (FISH). The neoplasm, which occurred in the kidney of a 35-year-old female, had an unusual, deceptively bland morphology consistent with myxoid monophasic synovial sarcoma.

MATERIALS AND METHODS

Immunohistochemistry for HMB45, cyclin D1, Estrogen receptor, BCOR, SATB2, CD34, cytokeratins AE1/3 and Cam5.2, epithelial membrane antigen (EMA), PAX8, S100 protein, melan A, desmin, smooth muscle actin, and ALK were performed as previously described[2,9]. This study was approved by the Institutional Review Boards at our institutions.

FISH on interphase nuclei from paraffin-embedded 4-micron sections was performed applying custom probes using bacterial artificial chromosomes (BAC) covering and flanking genes of interest. BAC clones for *SS18, SSX1, SSX2, SS18L1*, and *NEDD4* genes were chosen according to UCSC genome browser (http://genome.ucsc.edu), see Supplementary Table 1 and as previously described[10]. The BAC clones were obtained from BACPAC sources of Children's Hospital of Oakland Research Institute (CHORI)(Oakland, CA)(http://bacpac.chori.org). DNA from individual BACs was isolated according to the manufacturer's instructions, labeled with different fluorochromes in a nick translation reaction, denatured, and hybridized to pretreated slides. Slides were then incubated, washed, and mounted with

DAPI in an antifade solution, as previously described[10]. The genomic location of each BAC set was verified by hybridizing them to normal metaphase chromosomes. Two hundred successive nuclei were examined using a Zeiss fluorescence microscope (Zeiss Axioplan, Oberkochen, Germany), controlled by Isis 5 software (Metasystems, Newton, MA). A positive score was interpreted when at least 20% of the nuclei showed a split-apart signal in the break-apart assay. Nuclei with incomplete set of signals were omitted from the score.

RNA Sequencing

RNA was extracted from formalin-fixed paraffin-embedded (FFPE) tissue using Amsbio's ExpressArt FFPE Clear RNA Ready kit (Amsbio LLC, Cambridge, MA). Fragment length was assessed with an RNA 6000 chip on an Agilent Bioanalyzer (Agilent Technologies, Santa Clara, CA). RNA-sequencing libraries were prepared using 20 to 100 ng total RNA with the TruSight RNA Fusion Panel (Illumina, San Diego, CA). Each sample was subjected to targeted RNA sequencing on an Illumina MiSeq at 8 samples per flow cell (~3 million reads per sample). All reads were independently aligned with STAR (version 2.3) and BowTie2 against the human reference genome (hg19) for Manta-Fusion and TopHat-Fusion analysis, respectively.

RESULTS

Case Report

The patient was a 35-year-old female with a 5 × 4 × 4 cm renal tumor who underwent left radical nephrectomy. The neoplasm appeared grossly well delineated and solid. Microscopically, the spindle cell neoplasm demonstrating myxoid stroma (Figure 1), showing a scalloped border and permeating amongst native renal tubules at its edge. Focally, the tumor encircled the entrapped renal tubules in an 'onion skinning' or cuff-like pattern. The neoplastic spindle cells formed ill-defined fascicles and demonstrated elongated hyperchromatic nuclei with scant pale cytoplasm. Cellularity was extremely low in areas of pooled myxoid material. Pleomorphism and necrosis were absent and mitotic figures were sparse (<1 per 20 high power fields).

By immunohistochemistry, the neoplastic cells, but not the entrapped tubules, demonstrated diffuse nuclear labeling for TLE1 (Figure 1F) and cyclin D1. The neoplastic cells were negative for PAX8, cytokeratins (AE1/3 and Cam5.2), EMA, desmin, S100, HMB45, estrogen receptor, CD34, ALK, WT-1, BCOR, and SATB2. RT-PCR did not detect either the *SS18-SSX1* or *SS18-SSX2* gene fusions, though RNA quality was poor and considered inadequate. There was no evidence of a *BRAF* V600E mutation. Based upon the morphologic and immunohistochemical findings, the tumor was considered an unclassified mesenchymal neoplasm, possibly a low-grade spindle cell sarcoma though synovial sarcoma remained a strong consideration.

RNA sequencing and FISH validation

Targeted RNA sequencing revealed a novel *SS18-NEDD4* fusion transcript candidate, in which *SS18* exon 10 was fused to *NEDD4* exon 10 (Figure 2A). Based on this finding, custom BAC probes flanking *NEDD4* gene were designed (Supplementary Table 1) to

confirm this result. An *NEDD4* break-apart test showed split-apart between the red-centromeric and yellow-telomeric signals (Figure 2B, arrows). An *SS18* break-apart test showed a split between the red-centromeric and green-telomeric signals (Figure 2C, arrows).

By unsupervised clustering, the index case grouped closely with three other synovial sarcomas available on the same RNA-sequencing platform with canonical *SS18-SSX* fusions (data not shown). The platform included over 100 cases of various types of soft tissue and visceral sarcoma spanning over 20 different histologic types, including fusion positive as well as undetermined genotype. Of note, *BCOR* mRNA levels were not elevated, correlating with the absence of BCOR immunoreactivity noted in our case. *TLE1* mRNA could not be evaluated, since this gene was not represented on this RNA seq platform.

DISCUSSION

Primary renal synovial sarcoma was described in 2000[2] and has distinctive morphologic and molecular features. Most primary renal synovial sarcomas are monophasic spindle cell neoplasms that frequently entrap native renal tubules. The latter frequently undergo cystic dilatation, creating grossly cystic neoplasms[2]. Hypocellular cyst walls can simulate the bland walls of cystic nephroma, which lead many of these neoplasms to be characterized before the year 2000 as “sarcoma arising in cystic nephroma”[2]. Non-cystic renal synovial sarcomas were likely misclassified as monophasic stromal or biphasic stromal-epithelial Wilms tumor. Renal synovial sarcomas frequently present at advanced stage and have an aggressive clinical course, with approximately half of reported cases presenting with or developing metastases and only limited (less than 2 year) follow-up for those who did not. Moreover, approximately two-thirds of primary renal synovial sarcomas harbor the *SS18-SSX2* gene fusion, while the reverse is true for soft tissue tumors, where two-thirds of cases harbor the *SS18-SSX1* gene fusion[11]. The monophasic phenotype predominates in both anatomic sites[2,11].

In the current case, the diagnosis of renal synovial sarcoma was a leading consideration given the cytology and the TLE1 immunoreactivity, but the lack of specificity of the latter marker, minimal mitotic activity and the extensive myxoid change and hypocellularity precluded a definitive diagnosis. Extensive myxoid change in soft tissue synovial sarcoma is well documented, and frequently yields a hypocellular neoplasm that has a deceptively bland, low-grade appearance[12]. Myxoid synovial sarcoma can easily confused with benign myxoid neoplasms such as myxoid peripheral nerve sheath tumors (including perineurioma), myxoid solitary fibrous tumor, or low grade myxoid sarcomas such low-grade fibromyxoid sarcoma or myxoid dermatofibrosarcoma protuberans. However, myxoid primary renal synovial sarcoma has not previously been reported. In our case, a definitive diagnosis was made only after RNA sequencing yielded a *SS18-NEDD4* gene fusion.

The differential diagnosis included both benign and malignant neoplasms. While primary renal synovial sarcomas typically entrap renal tubules that dilate to form cysts, the current neoplasm entrapped renal tubules but was not associated with extensive cystic changes. Instead, the subtle scalloped border and concentric peritubular growth are characteristic of benign metanephric stromal tumor of the kidney[13]. The latter is considered part of the

spectrum of metanephric neoplasms of the kidney that also includes metanephric adenoma and metanephric adenofibroma[13]. All of the members of this family are associated with *BRAF* V600E mutations[14]. In the current case, the lack of CD34 immunoreactivity and *BRAF* V600E mutation argue against a metanephric stromal tumor. Other low-grade neoplasms in the differential diagnosis included myxoid solitary fibrous tumor (argued against by the lack of CD34 labeling) and myxoid nerve sheath tumor (argued against by the lack of labeling for S100 protein though these can be TLE1 positive). MEST of the kidney was also a consideration given its broad morphologic spectrum and the bland nature of the stroma, though the absence of fibrous or smooth muscular stroma, absence of ER immunoreactivity, and lack of complex epithelial patterns were not in keeping with this diagnosis. Clear cell sarcoma of the kidney, which also labels for TLE1, was excluded by the cytology, lack of branching capillary vasculature, and absence of BCOR immunoreactivity[15–17].

NEDD4 (Neuronal expressed developmentally downregulated four) belongs to the HECT (homologous to E6-AP/C-terminus) subfamily of ubiquitin protein ligases[18–21]. NEDD4 was initially discovered to have a role in central neuronal function and plasticity, but subsequently it has been found to have a role in the pathogenesis of human cancers. NEDD4 is upregulated in many cancers. The pro-oncogenic roles of NEDD4 include targeting PTEN for proteasomal degradation, which promotes PI3K/AKT signaling, along with stabilization of MDM2, which decreases p53 dependent transcription[18]. However, NEDD4 is also downregulated in some cancers such as pancreatic cancer and neuroblastoma, diminishing C-MYC proteasomal degradation, and thus promoting C-MYC-dependent growth programs[18]. Structural alterations of *NEDD4* in cancer are uncommon. Mutations in *NEDD4* are extremely rare, found in less than 5% of all cancers except uterine cancers in which it is seen in 8% of cases (www.cbioportal.org). Amplification and deletion are also uncommon, found in less than 3% of cases. Well-characterized cancer-associated gene fusions involving *NEDD4* have not previously been reported. Three analyses of thousands of tumors profiled in The Cancer Genome Atlas (TCGA) project identifies 6 potential *NEDD4* gene fusions. These include a fusion with *RDH10* in a squamous cell carcinoma of the lung, a fusion with *GABRA5* in a bladder cancer, fusions with *RFX7*, *ADMATSL3* and *RAB27A* in breast cancers, and a fusion with *MY05A* in a sarcoma[22–24].

In the current case, the gene fusion is predicted to fuse *SS18* exon 10 with *NEDD4* exon 10. The breakpoint within *SS18* is similar to that previously reported in synovial sarcomas with canonical fusions, resulting in retention of all but the C terminal 8 amino acids of the *SS18* transcriptional coactivator. *NEDD4* sequences include the approximately 500 C-terminal amino acids of NEDD4, including the ubiquitin ligase domain. Although the function of fusion protein is not entirely clear, we postulate that *NEDD4*, like *SSX1* or *SSX2*, fuses to *SS18* and converts this transcriptional coactivator to a transcriptional repressor, yielding a phenotype consistent with myxoid monophasic synovial sarcoma. Along these lines, the tumor clustered with other cases of synovial sarcoma on the same RNA-Seq platform. We considered the possibility that this neoplasm, despite the *SS18* rearrangement, might not represent a synovial sarcoma, just as not all neoplasms harboring *EWSR1* gene fusions represent Ewing sarcoma. Different gene fusion partners clearly can result in distinct neoplasms. While not all sarcomas harboring *SS18* gene fusions represent synovial

sarcomas (see below), the morphology, immunohistochemistry, and expression profile of this case supports our interpretation that it represents a primary renal myxoid synovial sarcoma.

Our case represents the second variant synovial sarcoma gene fusion described. Storlazzi et al. reported a t(X;20)(p11;q13) translocation resulting in a fusion of the related *SS18L1* gene (which is highly homologous with *SS18*) with *SSX1* in a biphasic intraneural synovial sarcoma of the leg in a 36 year old male[8]. Kao et al.[9] also reported a *SS18L1-SSX1* gene fusion in a monophasic spindle cell intraneural synovial sarcoma of the ankle of a 29-year-old female. The latter case demonstrated complex structural abnormalities of the Xp11.22–4 region and BCOR immunoreactivity[16] that initially suggested *BCOR* rearrangement.

In contrast, another fusion variant including the *SS18* gene was recently reported to occur in an undifferentiated round cell sarcoma, with Ewing-like morphology and strong CD99 immunopositivity[25]. Two such cases with *SS18-CRTC1* fusion occurring in the thigh of a 35-year-old male and the ankle of a 42-year-old female. The two tumors did not cluster together with other synovial sarcomas with the canonical *SS18-SSX* fusion, but rather closer to tumors harboring *EWSR1-CREB1* fusion (angiomatoid fibrous histiocytoma, primary pulmonary myxoid sarcoma) and showed distinct upregulation of NTRK1 at both mRNA and protein level. Based on these findings the authors suggest that undifferentiated tumors with *SS18-CRTC1* fusion variants most likely do not represent molecular variants of poorly differentiated synovial sarcoma.

In summary, we report a deceptively bland, myxoid primary renal synovial sarcoma with a novel *SS18-NEDD4* gene fusion. The bland morphology, low mitotic rate, and inability to detect typical *SS18-SSX1/2* gene fusions suggested alternative diagnoses, mainly benign neoplasms. This case illustrates the utility of RNA sequencing in classifying challenging neoplasms by identifying novel gene fusions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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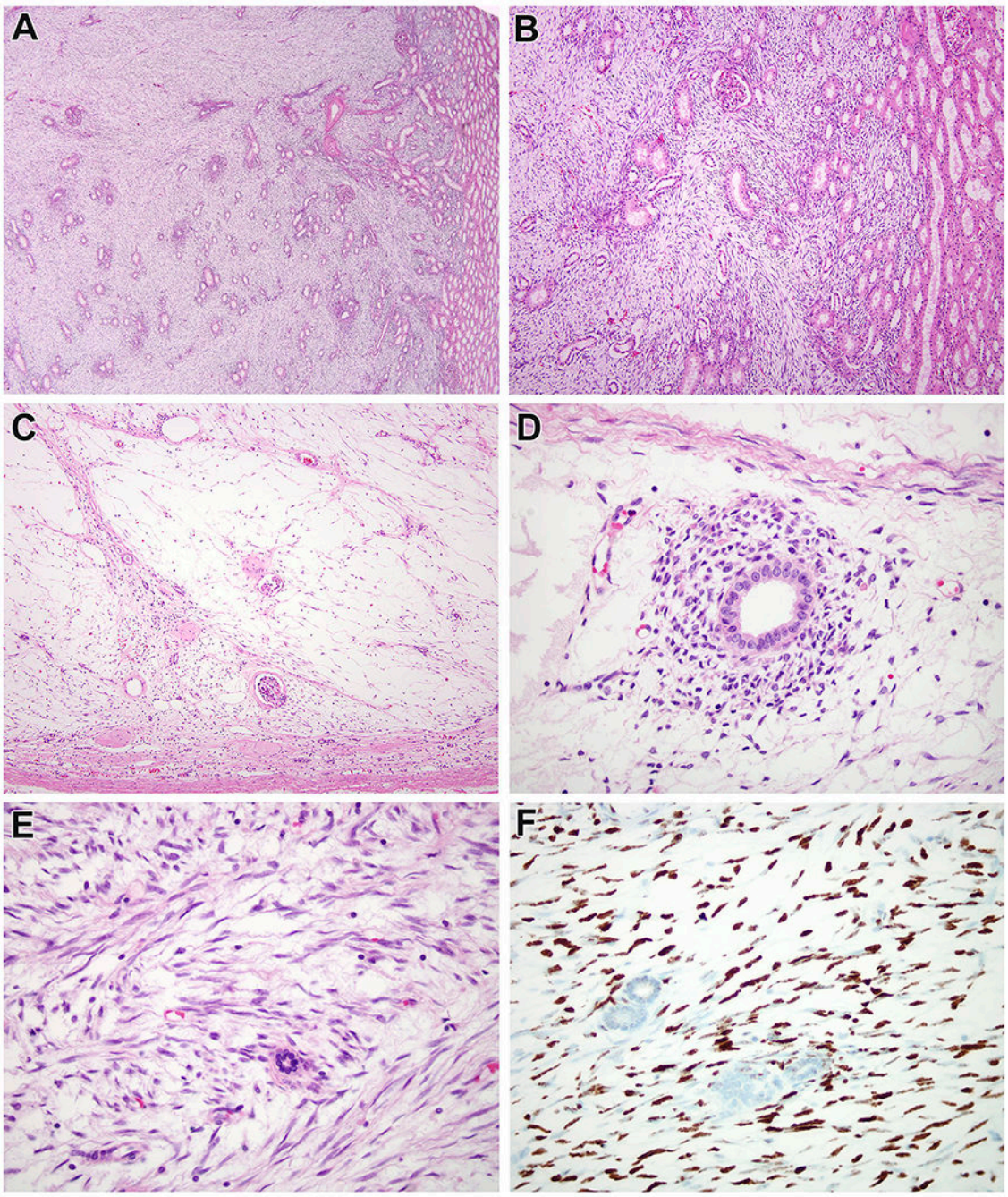

Figure 1:

The neoplasm was composed of a relatively hypocellular spindle cell proliferation associated with a prominent myxoid stroma, subtly infiltrating the adjacent kidney in a scalloped pattern (A, B). Some areas of the neoplasm were strikingly hypocellular and separated out individual tubules (C). The neoplasm condensed around native renal tubules in a concentric pattern (D). Other more cellular areas of the neoplasm featured poorly formed fascicles of spindle cells with elongated hyperchromatic nuclei (E). The neoplastic cells demonstrated strong nuclear labeling for TLE1, while entrapped native renal tubules were negative (F)

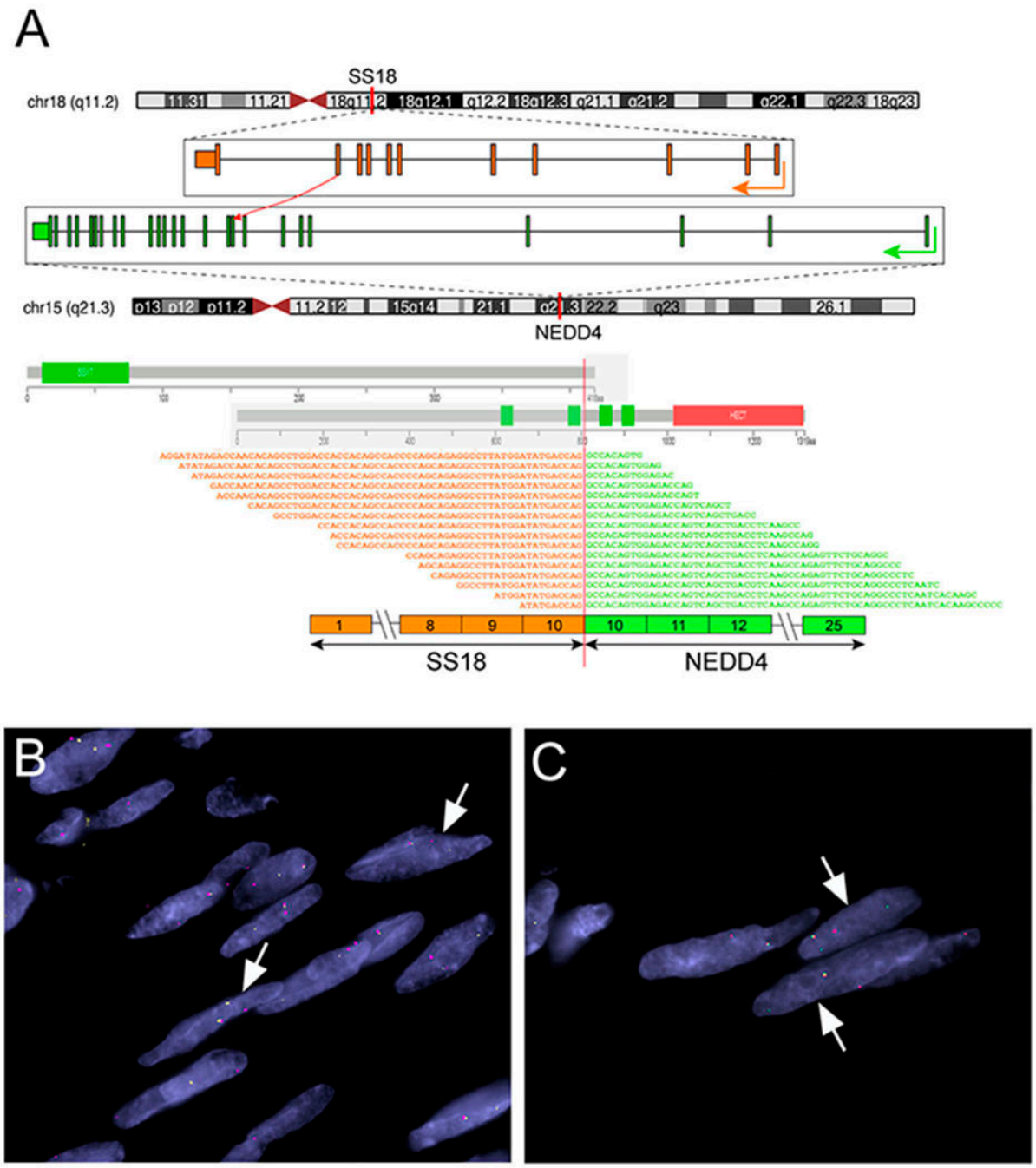

Figure 2:

SS18-NEDD4 gene fusion structure and molecular correlates. Diagrammatic representation of the *SS18* gene at 18q11 and the *NEDD4* gene at 15q21.3 (curved red arrow). Straight arrows show the direction of transcription of each gene. Junction reads from RNAseq data demonstrating the fusion of *SS18* exon 10 with *NEDD4* exon10. The protein domains of each gene involved are also schematically depicted. HECT represents the ubiquitin ligase domain of NEDD4 retained in the fusion protein (A). FISH break-apart assay showing

NEDD4 red centromeric split from the orange telomeric signals (B) and a *SS18* rearrangements with red centromeric split from the green telomeric signals (C).