SSX2 (Synovial Sarcoma, X breakpoint 2)

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Identity

Other names: CT5.2; HD21; HOM-MEL-40; MGC119055; MGC15364; MGC3884; RP11-552J9.2; SSX; SSX2A; SSX2B
HGNC (Hugo): SSX2
Location: Xp11.22

DNA/RNA

Description

The SSX2 gene locus encompasses 9 exons and 10,304 bp (Xp11; 52,752,974-52,742,671).

Transcription

The SSX2 gene is transcribed on the minus strand. 7 SSX2 mRNA splice variants (SV1-SV7) have been detected in liver, testis, skin melanoma, endometrium, choriocarcinoma, placenta, spleen of Hodgkins lymphoma.

Protein

Description

So far, two SSX2 protein isoforms (a and b) are known to exist. Their mRNAs correspond to SV1 (1466 bases) and SV3 (1322 bases) splice variants, respectively. The start codon for both isoforms is located in Exon 2. SSX2 isoform a is 233 amino acids (26.5 kD) and SSX2 isoform b 188 amino acids (21.6 kD). Of both isoforms, SSX2 isoform b is the most commonly seen and so far the best studied.

SSX2 Locus and mRNA Splice Variants. Note: Exons are drawn to scale.
**Expression**

SSX2 is a developmental nuclear protein normally expressed at high levels in testis (spermatogonia) and less abundantly in the thyroid gland. Its structural analysis revealed two functional domains; a 75 amino acids N-terminal region homologous to a Kruppel-associated box (KRAB) and a C-terminal 35 amino acids domain with a potent transcription repressor activity (SSXRD). KRAB boxes are usually present in zinc finger proteins and are implicated in transcription repression. SSX2 lacks DNA binding motifs and is thought to function in gene regulation through interaction with other transcription regulators. It contains a high density of charged amino acids (about 40%) and several consensus motifs for tyrosine phosphorylation and N-glycosylation.

**Function**

SSX2 is thought to function in development and germ line cells as a repressive gene regulator. Its control of gene expression is believed to be epigenetic in nature and to involve chromatin modification and remodeling. It is most likely mediated by the association of SSX2 with the Polycomb gene silencing complex at the SSXRD domain. Polycomb silencing involves chromatin compaction, DNA methylation, repressive histone modifications and inaccessibility of promoter regions to transcription machineries. Other SSX2-interacting partners include the LIM homeobox protein LHX4, a Ras-like GTPase Interactor, RAB3IP thought to be involved in vesicular transport, and SSX2IP, a putative cell cycle/ circadian rhythm regulator. Further studies will illuminate the mechanism by which these associations contribute to SSX2 nuclear function.

**Homology**

Human SSX2 is a member of a nine-gene family (SSX1, SSX2, SSX3, SSX4, SSX5, SSX6, SSX7, SSX8 and SSX9) located on the X chromosome. The SSX proteins are highly homologous at the nucleotide (about 90%) and the protein level (80%-90%). They are encoded by six exons and their expression is normally confined to testis. Recently, a mouse SSX gene family with 13 members and conserved KRAB and SSXRD domains has been identified.

**Implicated in**

**Synovial sarcoma**

**Note**

Synovial sarcoma (SS) is an aggressive soft tissue tumor that inflicts young adults between 15 and 40 years of age. Though its cell of origin is still unknown, it is thought to be a mesenchymal stem cell. Synovial sarcomas most frequently arise in the para-articular areas, but are also known to appear in other tissues such as the lung, heart, kidney, stomach, intestine, the abdomen, and the nervous system.

Synovial sarcoma is characterized by a unique chromosomal translocation event, t(X;18)(p11.2;q11.2) that involves a break in the SYT gene on chromosome 18 and another in a SSX gene on the X chromosome. When fusion occurs at the break-points, it generates a hybrid gene, SYT-SSX, which encodes a potent oncogene. SYT-SSX is thought to initiate tumorigenesis and contribute to the development of synovial sarcoma. The t(X;18) translocation is the hallmark of synovial sarcomas. SYT-SSX is present in over 95% of SS cases. Its presence in human tumors is therefore of considerable diagnostic value and is usually detected using FISH, RT-PCR, qPCR or real time PCR. Of the nine members of the SSX family, the SSX1 and SSX2 gene loci are the most frequent sites of breakage in SS, and occasionally SSX4. The break in SSX occurs at the beginning of exon 6. According to cDNA sequence data, the SSX2 component contained in the SYT-SSX oncogene consists of exons 6 and 8. They represent the last 78 amino acids of SSX2 isoform b. This region lacks the KRAB repressive domain but retains the SSXRD region. SS presents in two distinct morphologies, monophasic, populated by spindle tumor cells, and biphasic with an additional glandular epithelial component. Several studies have demonstrated a strong correlation between the translocation subtype, tumor morphology and the clinical course of the disease. While the majority of
SYT-SSX2-containing tumors were found to be monophasic, SYT-SSX1 was mostly detected in the biphasic tumors and was associated with a shorter metastasis-free period and a worse prognosis. However, the notion of the SYT-SSX subtype as a prognostic parameter influencing disease progression is still controversial due to contradictory data from later studies.

The molecular function of SYT-SSX is key to cancer development. The fusion of SSX to SYT results in the disruption of SYT and its associated chromatin-remodeling/coactivator complexes (SWI/SNF, p300) normal function in gene expression. This deregulation is caused by SSX aberrant epigenetic control that likely leads to untimely activation of oncogenic pathways such as IGF2, Wnt and ephrin, and reactivation of the anti-apoptotic oncogene, bcl-2.

**Hybrid/Mutated gene SYT-SSX2**

Note: SYT-SSX2 variants are rare. One was described by Fligman et al. It contains an additional 126 bp segment proximal to Exon 6, where the break occurred in Exon 5 while maintaining the frame.

**Cancer/testis antigen reactivated in several cancers.**

**Note**

SSX2 is the prototype of CT antigens (MAGE, GAGE, NY-Eso-1), a group of proteins normally expressed in testis, whose genes are located on the X chromosome and are, for reasons unknown, aberrantly reactivated in several cancers. NAME: CT antigen-SSX2, HOM-MEL40, CT5.2 THERAPY/TARGET/VACCINE: CT antigens are immunogenic and are expressed exclusively in tumor tissues. They are therefore considered optimal targets for tumor immunotherapy and vaccine development. Attempts at generating CD4+ and CD8+ T cells reactive to SSX2-specific peptides are underway.

**Disease**

SSX2 is expressed as a CT antigen in several Cancers: Skin melanoma, Breast cancer, Endometrial Cancer, Lung Cancer, Bladder Cancer, Head-Neck cancer, Synovial sarcoma, Multiple myeloma, colorectal carcinoma, Hepatocellular carcinoma, Prostate Cancer, Glioma, Stomach Cancer, Thyroid Cancer, Lymphoma, and Leukemia.

**Prognosis**

Expression of SSX2 and other CT antigens is associated with advanced metastatic cancer.

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