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Gene Section
Review

SSX2 (synovial sarcoma, X breakpoint 2)

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Identity

Other names: CT5.2, HD21, HOM-MEL-40, MGC119055, MGC15364, MGC3884, SSX, SSX2A, SSX2B

HGNC (Hugo): SSX2

Location: Xp11.22

DNA/RNA

Note
SSX2 is a member of a family of at least nine genes (SSX1, SSX2, SSX3, SSX4, SSX5, SSX6, SSX7, SSX8 and SSX9) and ten pseudogenes (ψSSX1-10), all arranged in two clusters on the X chromosome, except ψSSX10 (Gure et al., 2002).

Description

The SSX2 gene locus encompasses 9 exons and 10304 bp (Xp11; 52725946-52736249).

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

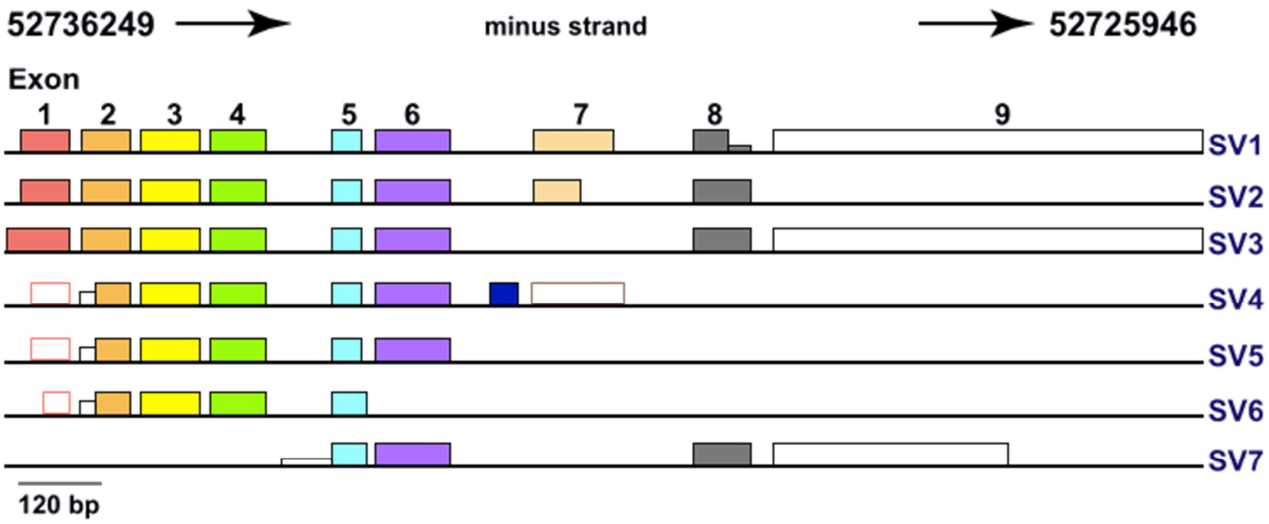
Note
SSX2 is gaining importance as a developmental factor involved in the pathogenesis of synovial sarcoma, and as an immunotherapeutic target for several human cancers.

Description

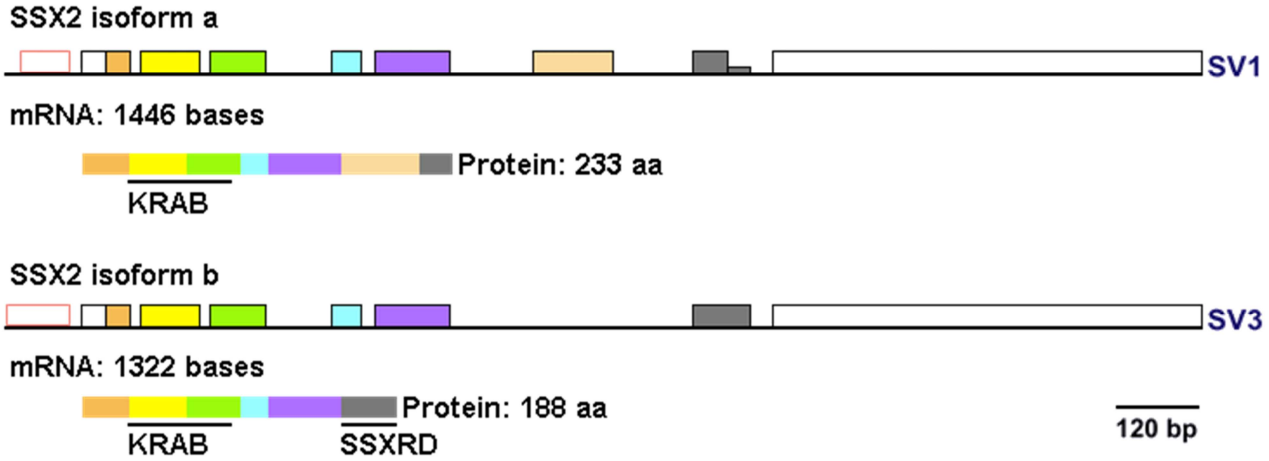
So far, two SSX2 protein isoforms (a and b) are known to exist.
Their mRNAs correspond to SV1 (1466 bases) and SV3 (1322 bases) splice variants, respectively.
The start codon for both isoforms is located in exon 2. SSX2 isoform a is 233 amino acids (26.5 kD) and SSX2 isoform b 188 amino acids (21.6 kD).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

Expression

SSX2 is a nuclear protein normally expressed at high levels in the developing and normal adult testis (Apale and B spermatogonia) (Chen et al., 2011; Lim et al., 2011), and less abundantly in the thyroid gland (Crew et al., 1995).
Its structural analysis (Lim et al., 1998) revealed two functional domains; an N-terminal region (amino acids 20-83) homologous to a Kruppel-associated box (KRAB) and a C-terminal 33 amino acids domain (amino acids 155-188) 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.



SSX2 locus and mRNA splice variants. Note: Exons are drawn to scale.



SSX2 protein isoforms. mRNAs and protein composition of SSX2 isoforms a and b. Open boxes are non-coding exons.

Localisation

SSX2 is usually localized in the nucleus (dos Santos et al., 2000).

However, cytoplasmic SSX2 was detected in pluripotent mesenchymal stem cells before differentiation (Cronwright et al., 2005).

Function

SSX2 is thought to function in germ line cell development (Chen et al., 2011) as a repressive gene regulator.

Its control of gene expression is believed to be epigenetic in nature and to involve chromatin modification and remodeling.

This is likely mediated by SSX2 association with the Polycomb gene-silencing complex at the SSXRD domain (Soulez et al., 1999; Barco et al., 2009; Przybyl et al., 2012), and with histones (Kato et al., 2002).

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 (de Bruijn et al., 2008), a Ras-like GTPase Interactor, RAB3IP (de Bruijn et al., 2002) thought to be involved in vesicular transport, and SSX2IP, a putative cell cycle/circadian rhythm regulator. SSX2IP expression on the surface of myeloid leukemia cells (AML) marks it as an appropriate target for AML immunotherapy (Breslin et al., 2007).

Recent evidence demonstrated a role for SSX2IP in promoting hepatocellular tumor metastasis and resistance to chemotherapy (Li et al., 2013).

Active studies are beginning to yield insights into SSX2 biological functions.

Recent evidence demonstrated a regulatory role for SSX2 in nuclear receptor signaling and cancer cell invasion (Chen et al., 2012).

A similar SSX2 effect on stem cell migration was reported previously (Cronwright et al., 2005).

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 (Gure et al., 1997; Gure et al., 2002).
Recently, a mouse SSX gene family with 13 members and conserved KRAB and SSXRD domains has been identified (Chen et al., 2003).

Implicated in

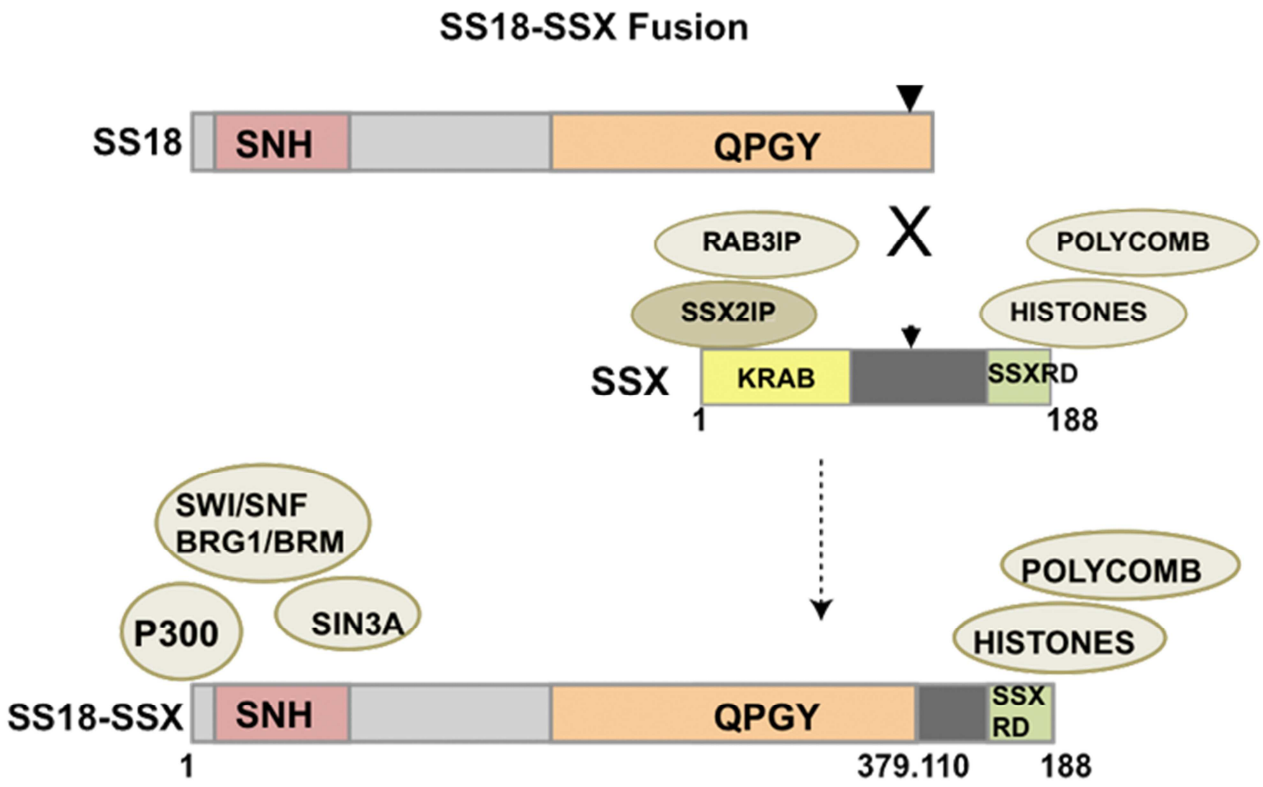
Synovial sarcoma

Note

Synovial sarcoma (SS) is an aggressive soft tissue tumor that afflicts 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 (Haldar et al., 2007; Naka et al., 2010).
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, head and neck, and the nervous system (Ferrari et al., 2008).
Synovial sarcoma is characterized by a unique chromosomal translocation event, t(X;18)(p11.2;q11.2) that involves a break in the SS18 gene on chromosome 18 and another in a SSX gene on the X chromosome.
When fusion occurs at the breakpoints, it generates a hybrid gene, SS18-SSX, which encodes a potent oncogene. SS18-SSX is thought to initiate tumorigenesis and contribute to the development of synovial sarcoma (Ladanyi, 2001; Przybyl et al., 2012).
The t(X;18) tanslocation is the hallmark of synovial sarcomas. SS18-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 (Amary et al., 2007; Ten Heuvel et al., 2008).
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 SS18-SSX2 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 (Crew et al., 1995; de Leeuw et al., 1995; Wei et al., 2003).
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 SS18-SSX2 containing tumors were found to be monophasic, SS18-SSX1 was mostly detected in the biphasic tumors and was associated with a shorter metastasis-free period and a worse prognosis (Kawai et al., 1998; Antonescu et al., 2000; Ladanyi et al., 2002; Fernebro et al., 2006). However, the notion of the SS18-SSX subtype as a prognostic parameter influencing disease progression is still controversial due to contradictory data from later studies (Guillou et al., 2004; Ladanyi, 2005).
The molecular function of SS18-SSX is key to cancer development (dos Santos et al., 2001; de Bruijn et al., 2007; Przybyl et al., 2012).
Fusion of SSX1/2 to SS18 results in the disruption of SS18 and its associated chromatin-remodeling/coactivator complexes (SWI/SNF, p300) normal function in gene expression (de Bruijn et al., 2006). SSX affinity for developmental genes controlled by Polycomb leads to the deregulation of such genes by SS18-SSX1/2 (Barco et al., 2009; Su et al., 2012). Deregulation of expression programs by SS18-SSX1/2 results in a series of biological events implicated in synovial sarcoma pathogenesis. These events likely include reprogramming of stem cell differentiation (Garcia et al., 2012), and untimely activation of oncogenic pathways such as IGF2 (Sun et al., 2006), Wnt (Horvai et al., 2006; Pretto et al., 2006; Bozzi et al., 2008), FGF (Ishibe et al., 2005; Garcia et al., 2012), and ephrin (Barco et al., 2007), as well as reactivation of the anti-apoptotic pathway and the bcl-2 oncogene (Mancuso et al., 2000, Jones et al., 2013).SS18-SSX2 variants are rare.
One was described by Fligman et al (1995). It contains an additional 126 bp segment proximal to SSX2 Exon 6, where the break occurred in Exon 5 while maintaining the frame.
Another SS18-SSX2 variant includes 50 additional base pairs of SSX2 Exon 5 (Otsuka et al., 2006).

Hybrid/Mutated gene

SS18-SSX2.



SS18-SSX fusion protein generated by the t(X;18)(p11.2;q11.2) chromosomal translocation. (X) represents cross-over. Arrowheads indicate breakpoints on SS18 and SSX.

Cancer / testis antigen reactivated in several cancers (CT antigen-SSX2, HOM-MEL40, CT5.2)

Note

SSX2 is a major prototype of CT antigens (e.g. MAGE, GAGE, NY-Eso-1), a group of proteins whose expression is restricted to testis and human cancers. A large subset of CT antigen genes (over 30), including the SSX family, are located on the X chromosome, and are, for reasons unknown, aberrantly reactivated in several major cancers. The complete absence of CT antigen expression in normal tissues renders them ideal targets for cancer immunotherapy (Gure et al., 1997; Simpson et al., 2005; Smith and McNeel, 2010; Lim et al., 2012).

Disease

Immunogenic response to reactivated SSX2 was first discovered in the sera of patients with malignant melanoma (Tureci et al., 1996). Since then aberrant expression of SSX2 has been detected in a large array of human cancers: skin melanoma (Tureci et al., 1998), breast cancer (Tureci et al., 1998; Mashino et al., 2001), endometrial cancer (Tureci et al., 1998), lung cancer (Gure et al., 2005), bladder cancer (Tureci et al., 1998), head-neck cancer (Tureci et al., 1998; Atanackovic et al., 2006), synovial sarcoma (Tureci et al., 1998), multiple myeloma (Taylor et al., 2005), colorectal carcinoma (Tureci et al., 1998; Scanlan et al., 2002), hepatocellular carcinoma (Chen et al., 2001; Bricard et al., 2005; Wu et al., 2006), prostate cancer (Dubovsky and McNeel, 2007; Smith and McNeel, 2011), glioma (Tureci et al., 1996, Tureci et al., 1998), stomach cancer (Mashino et al., 2001), thyroid cancer (Tureci et al., 1996), lymphoma (Tureci et al., 1998; Colleoni et al., 2002), leukemia (Niemeyer et al., 2003), neuroblastoma (Chi et al., 2002), osteosarcoma (Naka et al., 2002), ovarian cancer (Tureci et al., 1998; Valmori et al., 2006), and kidney cancer (Du et al., 2005).

Prognosis

In several cancers, SSX2 and other CT antigens are considered diagnostic and prognostic markers of advanced malignancy. In multiple myeloma, non-small cell lung cancer, prostate cancer, and colorectal cancer, their coordinate expression is correlated with markedly reduced survival (Dubovsky and McNeel, 2007; Gure et al., 2005; Taylor et al., 2005) and metastasis (Choi and Chang, 2012).

Immunotherapy:

The high immunogenicity of CT antigens and their tissue-restricted expression make them optimal targets for tumor immunotherapy and vaccine development. SSX2 is a major tumor antigen. Due to SSX2 wide expression in cancer, a single anti-SSX2 therapy will potentially benefit multiple diseases. Immunodominant

SSX2-derived peptides that elicit adequate T-cell responses have been identified, and initial reports have described their successful use in vivo (Wagner et al., 2003; Ayyoub et al., 2004a; Ayyoub et al., 2004b; Neumann et al., 2004; Ayyoub et al., 2005; Kyyamova et al., 2006; Huang et al., 2007; Neumann et al., 2011; Smith and McNeel, 2011). Since the majority of tumors express more than one CT antigen, attempts at generating polyvalent T cells directed against multiple epitopes for simultaneous antigen recognition are ongoing (Gerdemann et al., 2011; Smith et al., 2011). Notably, CT antigen-specific cytotoxic T lymphocytes were able to recognize and destroy chemoresistant lymphoma cells expressing the cognate antigens (Shafer et al., 2010). Finally, CT antigen directed immunotherapy could potentially become a valuable addition to chemotherapy for effective treatment of cancer.

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