Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Mini Review

SIX1 (sine oculis homeobox homolog 1) (mammalian)

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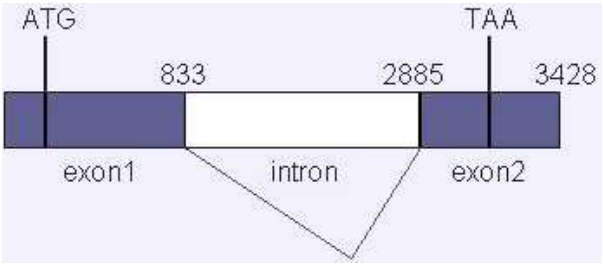
Identity

Hugo: SIX1
Other names: HSIX1 (human SIX1); Sine oculis (Drosophila homolog)
Location: 14q23

DNA/RNA



View of the SIX1 gene which is composed of 2 exons that are 833 and 543 bps respectively, and a single 2,052 bp intron. Start and stop codon positions are shown.

Description

The gene is composed of 2 exons and one intron and can be found on chromosome 14 at location 60,182,506 - 60,185,933.

Transcription

The transcript length is 1,376 base pairs and the start of the transcript is located in Contig AL049874.3.1.193047. The transcript can be detected in a variety of tissues during mouse development (see below for protein expression) and this has also been confirmed at the protein level (using reporter genes). The transcript is further detected throughout normal mouse mammary gland development with levels being the highest in the embryonic mammary gland and decreasing as the mammary gland differentiates in pregnancy and lactation. In the adult human, it is detected in skeletal muscle, pituitary gland, salivary gland, kidney, lung, and trachea.

Pseudogene

No.

Protein

View of the Six1 protein (total length 284 amino acids) that contains an N-terminal 115 amino acid Six domain (SD), and a 60 amino acid six-type homeodomain (HD). The SD is important for the interaction of Six1 with cofactors and also contributes to DNA binding along with the homeodomain.

Description

Six1 belongs to the Six family of homeoproteins. Amino acids: 284. Predicted Molecular Weight: 32210 Dalton. It exists as a phosphoprotein and is hyperphosphorylated in mitosis.

Expression

During mouse development, Six1 is expressed in otic vesicles, nasal placodes, branchial arches, Rathke[1]s pouch, dorsal root ganglion, proximal cranial ganglia, somites, cranial mesenchyme, nephrogenic cords, and limb mesenchyme. Six1 expression in muscles is present throughout myogenesis and into adulthood.

Localisation

Nuclear.

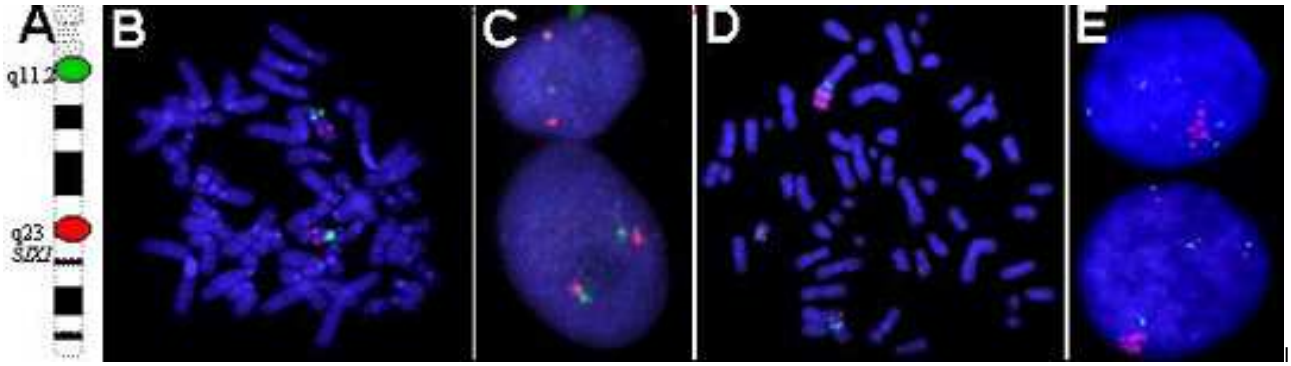


Diagram of chromosome 14 (A) showing location of the SIX1 gene at 14q23 (clone RP11-1042B17, labeled in SpectrumRed). Clone RPMI-324B11 (labeled in SpectrumGreen) mapped at 14q11.2 was used as control. Metaphase spread (B) and interphase nuclei (C) of the non-malignant, immortalized MCF10A cell line showing two normal copies of chromosome 14 with signals generated by the SIX1 and control FISH probes. Metaphase spread of the mammary carcinoma cell line, 21MT2 (D), showing a normal copy of chromosome 14 with SIX1 (red) and control probe (green), two derivative chromosomes carrying only the SIX1 or the SIX1 and control signals and a copy of the derivative 14 chromosome with SIX1 gene amplification. Interphase nuclei from 21MT2 cells with multiple copies of red and green signals, including a cluster of SIX1 signals representing gene amplification (E).

Function

Six1 is a transcription factor that is known to play a role in the proliferation and survival of precursor cells during normal development in numerous tissues including, amongst others, the kidney, inner ear, and muscle. It is also demonstrated to play a role in the proliferation of cancer cells and in cancer metastasis. It is known to activate several target genes, including cyclin A1, c-MYC, GDNF, and SLC12A2.

Mutations

Germinal

Germline mutations of SIX1 are observed in branchio-oto-renal sydrome, an autosomal dominant developmental disorder that is characterized by kidney and urinary tract malformations and hearing loss. The three SIX1 mutations identified to date all interfere with the ability of the Six1 protein to interact with its Eya1 cofactor, and two of the identified mutations additionally affect Six1-DNA binding.

Somatic

The SIX1 gene is amplified in about 5% of breast cancers (infiltrating ductal carcinomas).Overexpression of Six1 has been found in breast cancer, in Wilms[1]tumors, and in rhabdomyosarcoma.

Implicated in

Six1 is implicated in a number of cancers including breast cancer, rhabdomyosarcomas, and Wilms' tumors. It has also been implicated in branchio-oto-renal syndrome.

Note: Six1 is overexpressed in approximately 50% of primary breast cancers and 90% of metastatic lesions. Its overexpression in breast cancer has been linked to increased proliferation of breast cancer cells. Six1 is also a critical mediator of metastasis in a mouse rhabdomyosarcoma model.

Disease

Breast cancer, wilms' tumor, rhabdomyosarcoma, branchio-oto-renal syndrome,

Cytogenetics

The SIX1 gene is amplified in human breast cancer

Oncogenesis

SIX1 is overexpressed in several tumor types, including breast cancer, rhabdomyosarcomas, and Wilms' tumors. It has been implicated in both the proliferation and metastasis of tumor cells.

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