Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

FOXA1 (forkhead box A1)

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Published in Atlas Database: July 2010

Online updated version : http://AtlasGeneticsOncology.org/Genes/FOXA1ID44403ch14q21.html
DOI: 10.4267/2042/44994

Identity

Other names: HNF3A, MGC33105, TCF3A

HGNC (Hugo): FOXA1

Location: 14q21.1

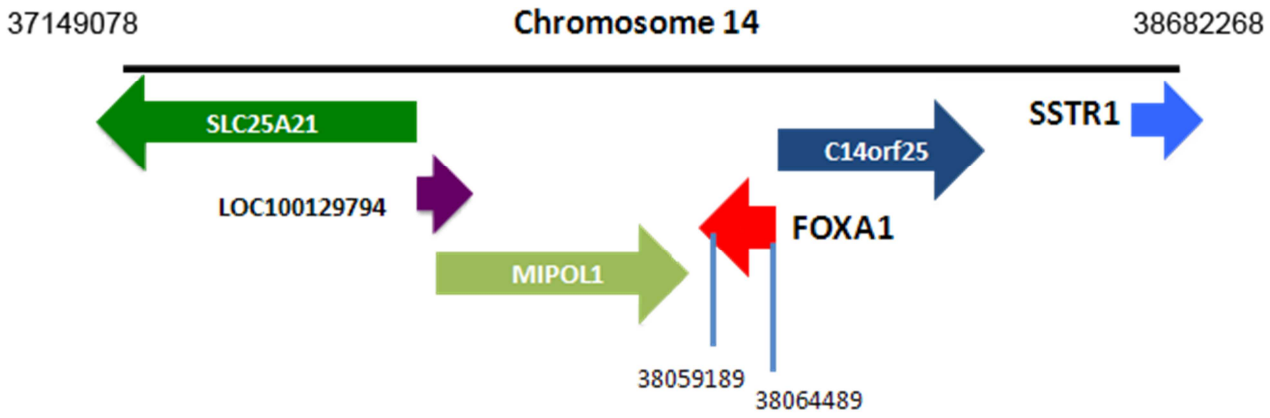
DNA/RNA

Description

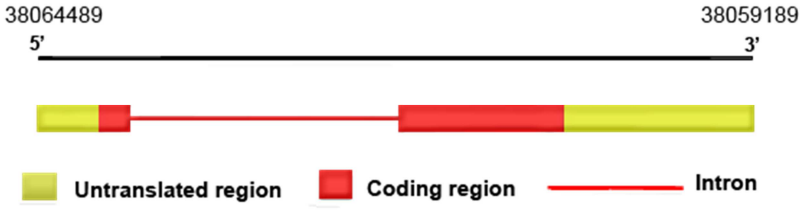
The transcribed region of FOXA1 extends only to 5400 bases and contains two exons and one intron. This gene is amplified in breast, esophageal, lung, and thyroid carcinomas. No deletions or chromosomal translocations have been reported. MIPOL1 and C14orf25 are the two adjoining genes. MIPOL1 has been described as a tumor suppressor gene in nasopharyngeal carcinoma, whereas the function of C14orf25 is unknown.

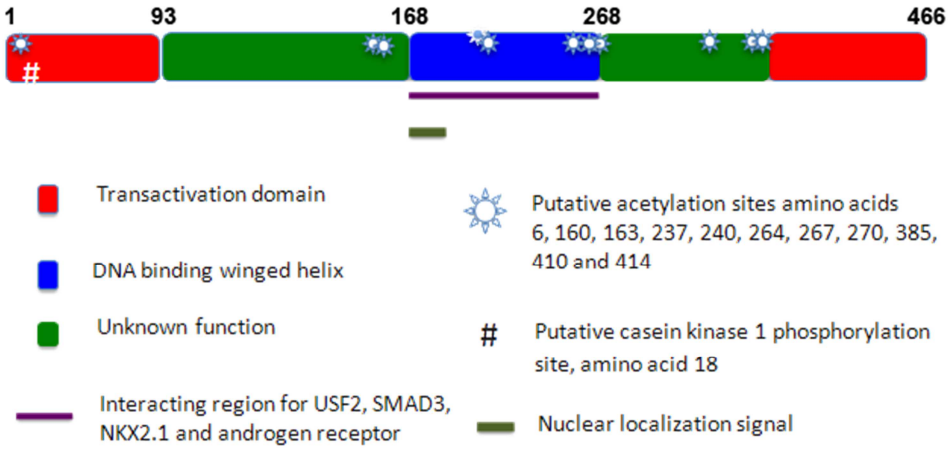
Transcription

FOXA1 is expressed predominantly in liver and is highly responsive to hormonal manipulation. Insulin suppresses its expression in embryonic stem cells as well as in breast cancer cells, whereas retinoic acid, estrogen, androgen, and heregulin induce its expression. The developmental transcription factors Oct-4 and SOX4 repress FOXA1 expression, whereas SOX17 and GATA-3 increase its expression. No splice variants have been reported. 542 base long promoter/enhancer is sufficient for liver-specific expression. This region binds to transcription factors TTF1 and NF-1. By binding to its own enhancer/promoter, FOXA1 autoregulates its expression. Peroxisome Proliferator Activated Receptor gamma also upregulates FOXA1 expression, although region of the promoter/enhancer involved in this upregulation is yet to be characterized.



FOXA1 is located on chromosome 14q21.1 and the transcribed region including an intron spans only 5300 bases. This protein binds to chromatinized DNA and, therefore, described as a "pioneer factor".





Protein

Description

FOXA1 is a 473 amino acid long transcription factor that binds to the consensus sequence A(A/T)TRTT(G/T)RYTY using the central region of the protein. Crystallography showed DNA binding domain in a winged helix-loop-helix configuration. Both N-terminus and C-terminus have transactivation domains. In silico analysis revealed 11 putative acetylation sites; acetylation sites in the DNA binding domain inhibit interaction with chromatin. The N-terminus has a putative caseine kinase 1 phosphorylation site.

Expression

FOXA1 was originally identified as a transcription factor that regulates gene expression in endoderm-derived tissues such as liver and lungs. Subsequent studies showed expression in pancreas, breast, prostate, bladder, intestine, and seminal vesicle. During embryogenesis, expression is seen in tissues derived from both foregut and hindgut endoderm (liver, lung, pancreas, stomach, intestine, prostate, and bladder). Organs derived from ectoderm (forebrain, floor plate, olfactory epithelium) and mesoderm (kidney, vagina, uterus, seminal and coagulating glands) also show expression. FOXA1 along with FOXA2 is required for normal bile duct development as deletion of FOXA1/2 in embryonic liver leads to hyperplasia of the billiary tree. Absence of FOXA1 in mammary gland leads to impaired ductal morphogenesis and reduction in the number of estrogen receptor-positive luminal epithelial cells.

Localisation

FOXA1 is localized predominantly in the nucleus. transforming growth factor beta 1 treatment results in cytoplasmic localization of the protein, which may be dependent on protein kinase C.

Function

FOXA1 binds to chromatinized DNA and opens the chromatin to allow binding of additional transcription factors. Specific histone modification such as histone H3 lysine 4 methylation guides recruitment of other factors. FOXA1 facilitates the recruitment of nuclear receptors including estrogen receptor, androgen receptor and glucocorticoid receptor. FOXA1 binding leads to both activation or repression of genes. These gene-specific effects involve interaction with or recruitment of other transcription factors such as SRC-3, USF2, TLE3, COUP-TFII, SHP, SMAD3, and HDAC7.

Homology

FOXA1 belongs to the 40-member FOX family of transcription factors. FOXA1, FOXA2, and FOXA3 form a subfamily and share a 110 amino acid long DNA binding domain with only 7 amino acid difference.

Mutations

Germinal

Coding region variation Ala83Thr, which is within the N-terminal transactivation domain, has been observed. However, this variation is not linked to breast cancer or maturity onset diabetes.

Implicated in

Breast cancer

Disease

Breast cancers that express estrogen receptor and progestrone receptor (ER+/PR+) demonstrate elevated FOXA1 expression. Amplification of the genomic region encompassing FOXA1 is also observed in ER+/PR+ breast cancer. A small subgroup of ER-/PR- negative breast cancers express FOXA1 and ER-/FOXA1- tumors show 3.6 fold enhanced recurrence rate compared to ER-/FOXA1+ tumors.

Prognosis

FOXA1-positivity ER+/PR+ breast cancer is associated with favorable prognosis.

Prostate cancer

Disease

FOXA1 is expressed in prostate cancer regardless of Gleason grade score and the expression is higher in metastatic disease. In transgenic animal models of prostate cancer, FOXA1 expression is seen in neuroendocrine carcinomas.

Pancreatic cancer

Disease

FOXA1 is expressed in normal and well-differentiated cancer but the expression is lost in undifferentiated cancer cells. Loss of FOXA1 expression correlates with epithelial-to-mesenchymal transition.

Esophageal squamous cell carcinoma

Disease

Cancers that have metastasized to lymphnodes express higher levels of FOXA1 along with its target gene KRT7.

Anaplastic thyroid carcinoma

Disease

Overexpressed in aggressive thyroid cancers and is amplified in these cancers. FOXA1 increases proliferation of these cells.

Diabetes

Disease

FOXA1 deficient mice are growth retarded and hypoglycemic due to defects in insulin secretion. However, the corresponding effects in human have not been reported.

Diet restriction-induced longevity

Note

PHA-4, the FOXA1, A2 and A3 ortholog in C. elegans is essential for diet-restriction-induced longevity.

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This article should be referenced as such:

Nakshatri H, Badve S. FOXA1 (forkhead box A1). Atlas Genet Cytogenet Oncol Haematol. 2011; 15(4):327-330.