Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

FOXO1 (Forkhead box O1)

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Published in Atlas Database: May 2008

Online updated version : http://AtlasGeneticsOncology.org/Genes/FOXO1ID83ch13q14.html
DOI: 10.4267/2042/44448

Identity

Other names: FKH1; FKHR; FOXO1A
HGNC (Hugo): FOXO1
Location: 13q14.11

DNA/RNA

Description

The FOXO1 gene extends approximately 110 kb and consists of 3 exons.

Transcription

Only a single transcript has been reported to be expressed from the FOXO1 gene, measuring 5.7 kb in length and containing an open reading frame of 1965 bp. At the RNA level, the gene is widely expressed.

Protein

Description

A single protein of 655 amino acids is expressed. This protein is a transcription factor with a forkhead box-containing DNA binding domain in the N-terminal region and an acidic, serine/threonine-rich transcriptional activation domain in the C-terminal region.

Expression

The protein is widely expressed. Covalent attachment of ubiquitin moieties (polyubiquitination) targets FOXO1 protein for degradation, and thus FOXO1 expression can be regulated by the ubiquitin-dependent proteasome. AKT is implicated in the regulation of FOXO1 expression by its enhancement of FOXO1 ubiquitination and proteolysis.

Localisation

The FOXO1 protein shuttles between the nucleus and cytoplasm. The subcellular localization and hence the transcriptional activity of FOXO1 is regulated by intracellular kinases. FOXO1 contains three AKT-phosphorylation motifs [RxRxx(S/T)]. Phosphorylation of these sites by AKT promotes nuclear exclusion, association with 14-3-3 adaptor proteins and cytosolic retention. The serum and glucocorticoid-inducible kinase (SGK), dual-specificity tyrosine-phosphorylated regulated kinase DYRK1A and cyclin-dependent kinase 2 (CDK2) may also similarly phosphorylate FOXO1 and contribute to its subcellular localization, thereby acting combinatorially to suppress FOXO1 transcriptional activity. Although the role of phosphatases in FOXO1 activation is unclear, PTEN may have a role in countering the effects of these kinases.

Function

FOXO1 plays an important role in many cellular processes. As a transcription factor, FOXO1 induces expression of target genes involved in apoptosis, glucose metabolism, cell cycle progression, and differentiation. There is increasing evidence of a role for FOXO1 as a tumor suppressor. FOXO1 transcriptional responses are also implicated in cellular protection following DNA damage and oxidative stress, which may be related to a role in longevity.

Homology

The first FOX transcription factor fork head was

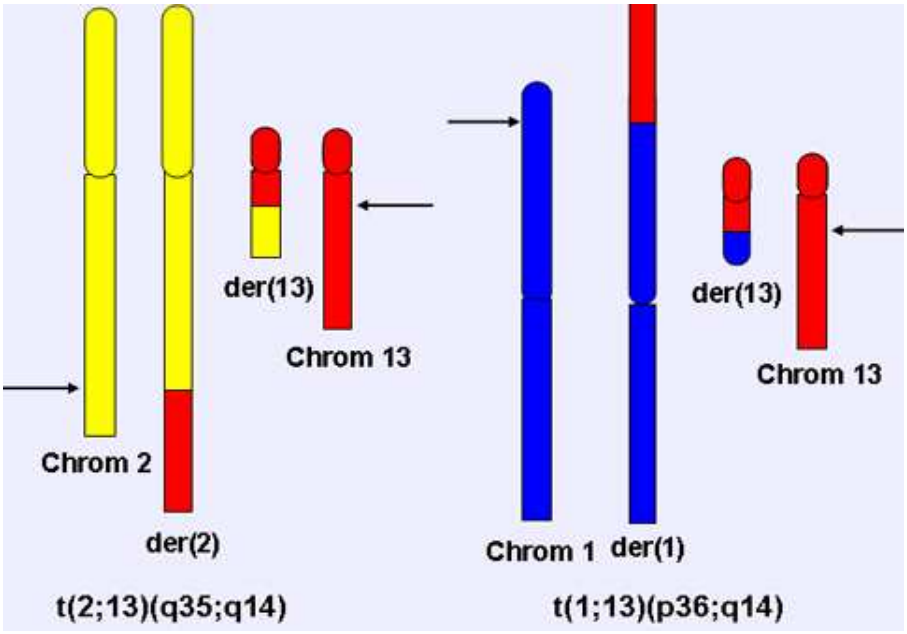


Figure 1. Diagram of t(2;13)(q35;q14) and t(1;13)(p36;q14) chromosomal translocations.

identified in Drosophila. The subsequent cloning of mammalian FOX transcription factors revealed a common DNA-binding domain (forkhead box) that is highly conserved across species including Drosophila melanogaster, C. elegans and Homo sapiens. Within the larger FOX transcription factor family, there is a subfamily of which FOXO1 is the prototype. Additional members of this FOXO subfamily are: FOXO3 (FKHRL1, FOXO2), FOXO4 (AFX), FOXO6. A gene homologous to FOXO subfamily members, daf-16, has also been identified in C. elegans and has facilitated analysis of the functional regulation of mammalian FOXO subfamily members. FOXO members share consensus phosphorylation motifs for multiple kinases including AKT, CDK2, DYRK1A and SGK. Phosphorylation of these motifs regulates subcellular localization, DNA affinity, and protein-protein interactions. Of note, three of the genes in the FOXO1 subfamily are involved in cancer associated-chromosomal translocations. In addition to the rearrangement of FOXO1 in alveolar rhabdomyosarcoma (discussed below), FOXO3 and FOXO4 are joined with the MLL gene by translocations in acute myeloid leukemias.

Mutations

Germinal

Inherited mutations of FOXO1 have not been identified.

Somatic

The FOXO1 gene is rearranged by the recurrent acquired chromosomal translocations - t(2;13)(q35;q14) and t(1;13)(p36;q14) - in the myogenic soft tissue cancer alveolar rhabdomyosarcoma. As a result of the 2;13 or 1;13 translocation, portions of the PAX3 or PAX7 gene (on chromosomes 2 or 1, respectively) are juxtaposed with portions of the FOXO1 gene. In particular, the 5' region of PAX3 or PAX7, including the first seven exons of either gene, is joined to the 3' region of FOXO1, including its last two exons. Though the reciprocal chimeric gene is also generated, the PAX3-FOXO1 and PAX7-FOXO1 chimeric genes are more consistent and highly expressed, and result in expression of fusion proteins consisting of the intact PAX3 or PAX7 N-terminal DNA binding domain fused in-framed to the intact FOXO1 C-terminal transcriptional activation domain.

FOXO1 was identified as only gene within a minimal common region of deletion in chromosomal region 13q14 in prostate carcinoma. FOXO1 deletion was detected in about 30% of prostate cancer samples, and additional cases were identified with reduced expression without evidence of deletion. Based on functional testing in prostate cancer cell lines that indicated that FOXO1 affected cell proliferation, survival, and androgen receptor signaling, the combined data indicates that FOXO1 is a tumor suppressor gene in prostate cancer.

Implicated in

Alveolar Rhabdomyosarcoma (ARMS)

Disease

ARMS is one subtype of a family of pediatric soft tissue tumors that is related to the skeletal muscle lineage. In contrast to embryonal rhabdomyosarcoma (ERMS), the other major subtype in this family, ARMS often occurs in adolescents and young adults, with

primary tumors located in the vicinity of skeletal muscle, such as in the extremities and trunk.

Prognosis

The overall prognosis for patients with ARMS is less favorable compared to those with ERMS. The three year survival rate for patients without metastatic disease was 66% (IRS-IV clinical trial), and evidence of metastasis decreased the survival rate to only 16%. The pathogenesis of metastatic ARMS is associated with an early and wide dissemination, often involving bone marrow, and to poor response to chemotherapy. One study also indicates that for metastatic patients, tumors with a PAX3-FKHR fusion have a poorer outcome than tumors with a PAX7-FKHR fusion. In contrast, there is no reported difference in outcome between these subtypes in patients with non-metastatic tumors.

Cytogenetics

Translocations involving the q14 band on chromosome 13 and the q35 band on chromosome 2 - t(2;13)(q35;q14) - distinguish ARMS from other soft tissue sarcomas. An additional 1;13 translocation - t(1;13)(p36;q14) - has been identified in a smaller number of ARMS cases.

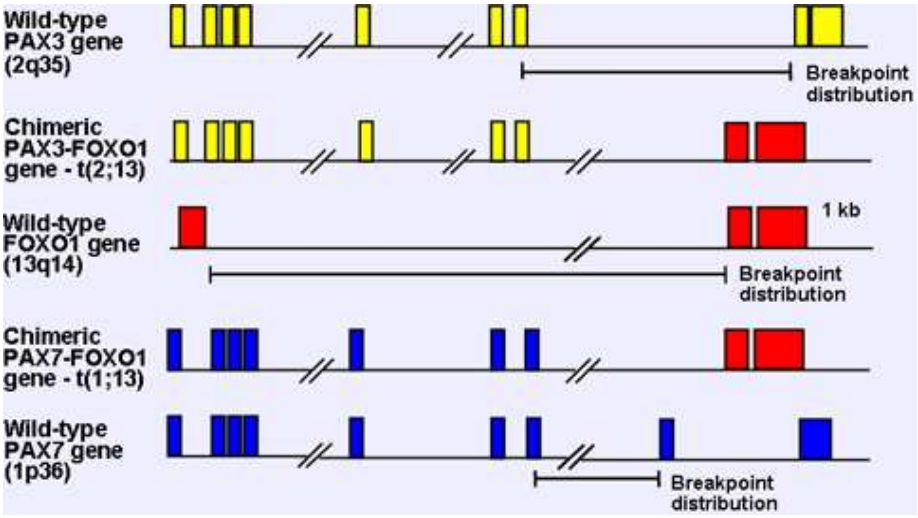


Figure 2. Generation of chimeric genes by the 2;13 and 1;13 translocations in ARMS. The exons of the wild-type and fusion genes are shown as boxes above each map and the translocation breakpoint distributions are shown as line segments below the map of the wild-type genes.

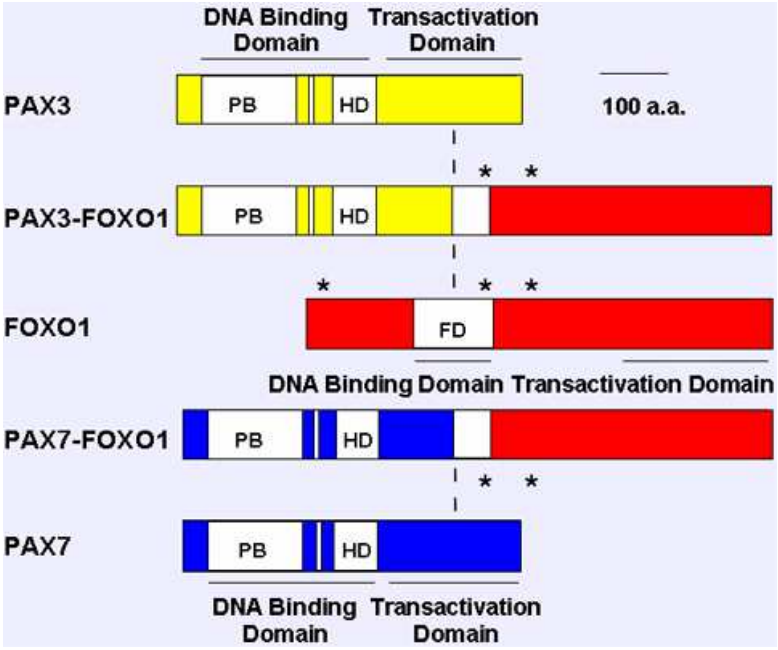


Figure 3. Comparison of wild-type and fusion products associated with the 2;13 and 1;13 translocations. The paired box, octapeptide, homeobox and fork head domain are indicated as open boxes, and transcriptional domains (DNA binding domain, DBD; transcriptional activation domain) are shown as solid bars. The sites phosphorylated by Akt are indicated by stars. The vertical dash line indicates the translocation fusion point.

Prostate carcinoma

Disease

Adenocarcinoma of the prostate is a malignant tumor arising from the glandular epithelium of the prostate gland.

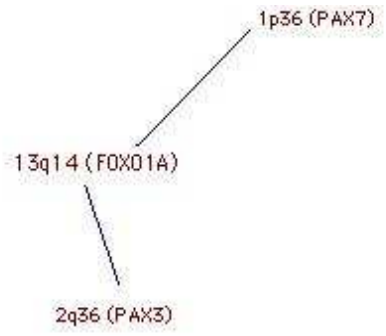
Prognosis

In several studies in prostate cancer correlating outcome and chromosomal changes detected by allelic loss or comparative genomic hybridization, deletions or losses involving chromosomal region 13q14 were not found to be correlated with significant differences in outcome.

Cytogenetics

One of the most frequent deletions in prostate cancer involves the q arm of chromosome 13. There are two common regions of deletion in the q arm of chromosome 13: 13q14 and 13q21.

Breakpoints



FOXO1A and partners. Editor 08/2005; last update 05/2008

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This article should be referenced as such:

O'Connor R, Barr FG. FOXO1 (Forkhead box O1). Atlas Genet Cytogenet Oncol Haematol. 2009; 13(4):268-272.