

Gene Section

Review

FOXC1 (forkhead box C1)

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Identity

Other names: ARA, FKHL7, FREAC-3, FREAC3, IGDA, IHG1, IRID1, RIEG3

HGNC (Hugo): FOXC1

Location: 6p25.3

DNA/RNA

Description

Orientation: Plus strand. Genomic Size: 3447 bases.
Exon Count: 1. Coding Exon Count: 1. RefSeq DNA sequence: NC_000006.11- NT_007592.15 contains Fork Head domain (FHD).

Basal Isoelectric point: 8.7.

Transcription

Gene is transcribed into 3454 bps mRNA, containing one exon.

Protein

Description

Sequence length: 553 amino acids, mass: 56789 Dalton.

It contains one Fork Head DNA binding domain, consists approximately of 110 amino acids. FHD is a conservative sequence shared by all FOX proteins.

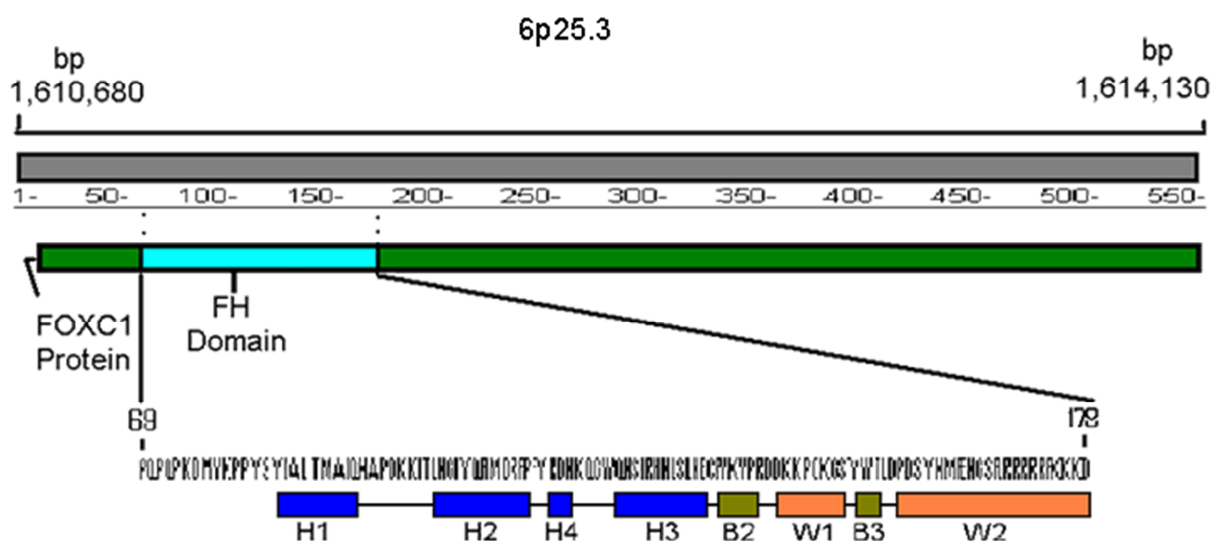


Figure1: Gene sequence (grey) and transcriptional product of FOXC1. Forkhead DNA binding domain (FH Domain) contains 4 alpha helices (H1, H2, H4 and H3), 2 beta sheets (B2 and B3) and two wings (W1 and W2).

2009) found out that Fox genes have evolved to acquire a specialized function in many key biological processes. Mutations in Fox genes have a profound effect on human disease, causing phenotypes as varied as cancer, glaucoma and language disorders.

Mutations

Germinal

Deletion of distal 6p is associated with a distinctive clinical phenotype including Axenfeld-Rieger malformation, hearing loss, congenital heart disease, dental anomalies, developmental delay, and a characteristic facial appearance.

By DNA sequencing of FOXC1 in 5 families and 16 sporadic patients a 6p microdeletion resulted from a de novo 6:18 translocation was recognized. The same translocation was reported in a child with specific ocular and facial phenotype (Maclean et al., 2005). Detailed analysis confirmed deletion of the FOXC1, FOXF2 and FOXQ1 forkhead gene cluster at 6p25. It showed central nervous system (CNS) anomalies, including hydrocephalus and hypoplasia of the cerebellum, brainstem, and corpus callosum with mild to moderate developmental delay.

The mouse gene Mf1 is homolog of FOXC1. Homozygous null Mf1-lacZ mice die at birth with hydrocephalus, eye defects, and multiple skeletal abnormalities identical to those of the classic mutant, congenital hydrocephalus. Kume et al. (1998) showed that congenital hydrocephalus involves a point mutation in Mf1, generating a truncated protein lacking the DNA-binding domain. Mesenchyme cells from Mf1-lacZ embryos differentiated poorly into cartilage in micro-mass culture and did not respond to added BMP2 and TGF-beta-1. The differentiation of arachnoid cells in the mutant meninges was also abnormal.

Somatic

Using genotyping and FISH as method of investigations, Lehmann et al. (2002) studied a 9-generation Scottish family segregating autosomal dominant iridogoniodysgenesis. The team found an interstitial duplication of chromosome 6p25 which encompassed the FOXC1 gene.

Nishimura et al. (2001) analyzed the coding region of the FOXC1 gene in 70 probands with congenital anterior chamber defects and detected 9 mutations, 8 of which were novel. Affected members from 2 families, one with iris-hypoplasia and the other with Peters anomaly, had 2 different partial duplications of 6p25, respectively, both encompassing the FOXC1 gene. These data suggested that both FOXC1 haploinsufficiency and increased gene dosage may cause anterior-chamber defects of the eye.

Fetterman et al. (2009) identified a heterozygous FOXC1 missense mutation outside of the forkhead

domain, and in the inhibitory domain, in 2 unrelated patients with iridogoniodysgenesis. Iridogoniodysgenesis phenotype is more commonly associated with FOXC1 duplications than point mutation.

Honkanen et al. (2003) identified the F112S (a point mutation in the FOXC1 gene in 5 affected members of a 4-generation family segregating autosomal dominant anterior segment defects, including a patient who also had Peters anomaly.

Saleem et al. (2001) investigated 5 missense mutations of the FOXC1 transcription factor found in patients with Axenfeld-Rieger malformations to determine their effects on FOXC1 structure and function.

Molecular modelling of the FOXC1 fork head domain predicted that the missense mutations did not alter FOXC1 structure.

Biochemical analyses indicated that whereas all mutant proteins correctly localized to the cell nucleus, the I87M mutation reduced FOXC1 protein levels. DNA-binding experiments revealed that although the S82T and S131L mutations decreased DNA binding, the F112S and I126M mutations did not.

However, the F112S and I126M mutations decreased the transactivation ability of FOXC1. Saleem et al. (2003) studied an additional 5 missense mutations in the FOXC1 gene. Biological analyses indicated that all missense mutations studied caused various FOXC1 perturbations, including nuclear localization defects, reduced or abolished DNA binding capacity, and a reduction in the transactivation capacity of FOXC1.

Implicated in

Breast cancer

Note

Methylation status of FOXC1 promoter can be related to invasiveness of breast cancer and patient survival.

Higher methylation means lower expression and more invasiveness of tumour, in advanced breast tumors as concluded by Dejeux et al. (2010) and Muggerud et al. (2010) methylation levels of FOXC1 were higher in oestrogen receptor (ER) positive vs. ER negative tumours; whereas methylation levels lower in tumours with a TP53 mutation. FOXC1 showed a significant increase in the methylation frequency in invasive tumours. Low FOXC1 gene expression in both methylated and unmethylated DCIS (ductal carcinoma in situ) and IDCs (invasive ductal carcinomas) indicates that the loss of expression of FOXC1 happens at earlier stage during the progression of breast cancer.

Prognosis

Recently FOXC1 has been reported as potential prognostic biomarker with functional significance in basal like breast cancer by Ray et al. (2010) and Dejeux et al. (2010).

Invasive carcinoma

Oncogenesis

Zhou et al. (2002) showed that TGF-beta1 up regulated transcription of FOXC1 in a number of human cancer cell lines. In FOXC1 homozygous knockdown (-foxc1/-foxc1) HeLa cell line, ectopic expression of FOXC1 cDNA restored the potential of TGF-beta1 to inhibit cell growth by arresting cells in the G0/G1 phase. Which reveals the FOXC1 having a tumour suppressive function. Furthermore, screens of primary endometrial and ovarian cancers revealed that FOXC1 was deleted in 6.7% out of 11.7% transcriptional silenced primary cancers. It suggests that FOXC1 functions as a tumour suppressor through TGF-beta1 mediated signals.

Van der Heul-Nieuwenhuijsen et al. (2009) analysed a set of 12 different FOX genes, including FOXC1, by quantitative reverse transcription-polymerase chain reaction in prostate zones, prostate cancer, lymph node metastases, benign prostatic hyperplasia (BPH), xenografts and several prostate cell lines. Various members of the FOX family were differentially expressed in the zones of the normal prostate and in benign and malignant out-growths.

The expression profiles of FOXF1 and FOXF2 suggest a role in epithelial to mesenchymal transition, while FOXA1 and FOXC1 expression is linked to androgen-associated growth status of cancer.

FOXC1 contribute to microvascular invasion in primary hepatocellular carcinoma, making FOXC1 a candidate predictive marker of microvascular invasion. Inhibition of FOXC1 may reduce tumour metastasis in hepatocellular carcinoma (liver cancer) (Xu et al., 2012).

Axenfeld-Reiger Syndrome (ARS) or Axenfeld-Reiger syndrome type 3 (RIEG3) also known as Axenfeld syndrome or Axenfeld Anomaly

Note

Phenotype may show posterior corneal embryotoxon, prominent Schwalbe line and iris adhesion to the Schwalbe line. It may also show hypertelorism, hypoplasia of the malar bones, congenital absence of some teeth and mental retardation. Tooth anomalies are associated with Reiger syndrome. Glaucoma may occur in almost fifty percent of the patients with Axenfeld-Reiger malformations (Ito et al., 2007).

Cytogenetics

As results of different studies of ARS/ RIEG3 cases: Nishimura et al. (1998) found an 11-bp deletion upstream of the FOXC1 forkhead domain. The team also identified a C-to-T transition within the forkhead domain, causing a ser131-to-leu (S131L) amino acid substitution. The Nishimura team found a C-to-G transversion within the forkhead domain. This change resulted in an ile126-to-met (I126M) amino acid

substitution. They also identified a T-to-C transition in the FOXC1 gene that resulted in a phe112-to-ser (F112S) transition within the forkhead domain.

Mirzayans et al. (2000) found that Axenfeld-Rieger syndrome (RIEG3) was associated with a 67C-T transition in the FOXC1 gene, predicted to cause a gln23-to-ter (E23X) substitution upstream of the forkhead domain.

Nishimura et al. (2001) found a 22-bp insertion from position 26 through 47 in the cDNA of the FOXC1 gene.

Mears et al. (1998) identified heterozygosity for a 245G-C transversion in the FOXC1 gene, predicted to result in a ser82-to-thr (S82T) substitution at the start of helix 1 of the forkhead domain. They also identified a 261C-G transversion in the FOXC1 gene, resulting in an ile87-to-met (I87M) substitution in helix 1 of the forkhead domain.

Ito et al. (2007) identified a heterozygous 388C-T transition in the FOXC1 gene, resulting in a leu130-to-phe (L130F) substitution in helix 3, the so-called 'recognition helix' of the forkhead domain.

Weisschuh et al. (2008) identified heterozygosity for a 358C-T transition in the FOXC1 gene, resulting in a gln120-to-ter (Q120X) substitution causing truncation of part of the forkhead domain.

Peters anomaly (PA) and Iridogoniodysgenesis anomaly (IGDA)

Note

IGDA is an autosomal dominant phenotype characterized by iris hypoplasia, goniodysgenesis, and juvenile glaucoma.

Peters anomaly consists of a central corneal leukoma, absence of the posterior corneal stroma and Descemet membrane, and a variable degree of iris and lenticular attachments to the central aspect of the posterior cornea (Honkanen et al., 2003).

Cytogenetics

As results of different studies of PA and IGDA cases: Lehmann et al. (2000) found by genotyping of FOXC1, with microsatellite repeat markers, the presence of a chromosomal duplication.

Nishimura et al. (2001) identified a partial duplication of chromosome 6p25, which encompassed the FOXC1 gene.

Fetterman et al. (2009) identified heterozygosity for an 889C-T transition in the FOXC1 gene, resulting in a pro297-to-ser (P297S) substitution in the inhibitory domain.

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