Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section

Review

FOXE1 (forkhead box E1 (thyroid transcription factor 2))

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Published in Atlas Database: May 2010

Online updated version : http://AtlasGeneticsOncology.org/Genes/FOXE1ID47197ch9q22.html
DOI: 10.4267/2042/44963

Identity

Other names: FKHL15, FOXE2, HFKH4, HFKL5, TITF2, TTF-2, TTF2

HGNC (Hugo): FOXE1

Location: 9q22.33

DNA/RNA

Description

The gene consists of 1 exon and is intronless; the 5' and the 3' parts of the exon are non-coding.

Transcription

3461 bp transcript with a 1121 bp of coding sequence.

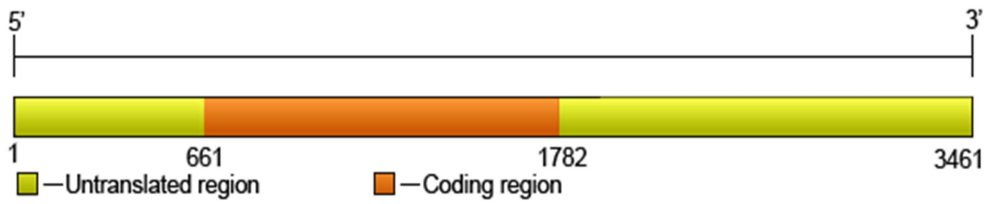
Protein

Description

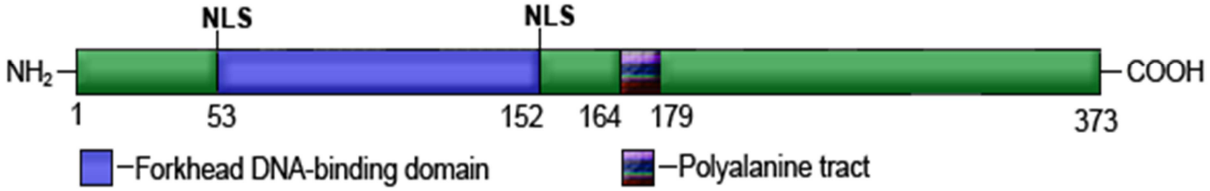
The FOXE1 protein is 373-amino acid long and its molecular weight is 42 kDa. It contains a forkhead DNA-binding domain, 2 putative nuclear localization signals (NLS) which flank the DNA-binding domain, and a polyalanine (polyA) stretch of variable length. Population-based studies found polymorphism of the polyA tract lengths varying from 11 to 19 residues with the 14 as the most frequent allele (Venza et al., 2006; Macchia et al., 1999; Hishinuma et al., 2001; Tonacchera et al., 2004; Santarpia et al., 2007; Carre et al., 2007).

Expression

In humans, FOXE1 is expressed at the embryonic Carnegie stage (CS) 15 in the thyroid primordium and persists in the thyroid gland throughout development. At the same embryonic stage, FOXE1 is also detectable in the thymus and in the oropharyngeal epithelium. At 11 weeks of development it is present in the tracheal and esophageal epithelium (Trueba et al., 2005).
In mice, FOXE1 is expressed at embryonic day E8.5 in the endoderm corresponding to the floor of the foregut, at E9.2-9.3 in the epithelium lining the anterior foregut and the posterior stomodeum, including the pharyngeal membrane, and in the migrating thyroid primordium and at E9.5 in the craniopharyngeal ectoderm involved in palate formation. Later, at E10.5 FOXE1 expression is transcribed along all the endoderm of the foregut lining the visceral pouch of the branchial arches (Zannini et al., 1997; Dathan et al., 2002).



Schematic diagram of the human FOXE1 gene.



Diagrammatic representation of the functional domains of human FOXE1 protein.

Localisation

Nuclear.

Function

FOXE1 regulates the transcription of thyroglobulin (Tg) and thyroid peroxidase (TPO), and represses transcriptional activation of TTF-1 and PAX8 on the Tg and TPO promoters. The gene plays an important role in thyroid development, secondary palate closure and hair follicle morphogenesis. FOXE1 is also implicated in malignancy.

Homology

Member of the forkhead box E (FOXE) subfamily which itself is a part of the large FOX gene family of transcription factors, characterized by sharing a common 100 amino acid forkhead domain. FOXE proteins (FOXE-1, -2, -3, -4) are widely expressed in a range of tissues, have diverse roles in development and metabolism and have been implicated in various forms of cancer and disease.

Implicated in

Thyroid carcinoma

Disease

Genome-wide association studies (GWAS) showed a significant correlation of the rs965513 variant located 57-kb upstream to FOXE1 with follicular thyroid carcinoma (FTC) (Gudmundsson et al., 2009) as well as with sporadic or radiation-related papillary thyroid carcinoma (PTC) (Gudmundsson et al., 2009; Takahashi et al., 2010). A detailed analysis of the PTC-risk conferring haplotype identified rs1867277 as a highly correlated putative functional variant within the FOXE1 promoter (Landa et al., 2009). Functional assays revealed that the rs1867277 G allele partially impairs the recruitment of USF1 and USF2 factors to the FOXE1 promoter and alters the expression status of the FOXE1 gene (Landa et al., 2009).

Pancreatic cancer

Disease

Aberrant CpG methylation of FOXE1 was detected in pancreatic cancer cell lines and in a series of resected primary pancreatic carcinomas (Sato et al., 2003) as well as in familial and sporadic pancreatic adenocarcinoma specimens (Brune et al., 2008). FOXE1 was also prevalently methylated in the surgical pancreatic juice of patients with pancreatic ductal adenocarcinoma, less frequently in samples of intraductal papillary mucinous neoplasms, but never in patients with chronic pancreatitis (Matsubayashi et al., 2006).

Breast cancer

Disease

DNA hypermethylation events in the CpG islands of FOXE1 promoter were present in plasma samples from breast cancer patients (Weisenberger et al., 2008).

Cutaneous squamous cell carcinoma (SCC)

Disease

A higher frequency of FOXE1 promoter hypermethylation was found in cutaneous SCCs (55%), as compared with the adjacent uninvolved skin (12%) and blood control samples (9%). FOXE1 methylation was frequently seen in association with a complete absence or downregulation of gene expression. Treatment with the demethylating agent 5-Aza-2'-deoxycytidine resulted in profound reactivation of FOXE1 expression (Venza et al., 2010a). It was also reported that expansions of the polyA tract (16 alanine) of FOXE1 predisposes to cutaneous SCC (Venza et al., 2010b).

Bamforth-lazarus syndrome

Disease

Homozygous, human loss-of-function mutations located within the forkhead domain of FOXE1 (A65V, S57N and R72S) cause the Bamforth-Lazarus syndrome, which includes congenital hypothyroidism, cleft palate and spiky hair, with or without choanal atresia, bifid epiglottis, and ocular hypertelorism, depending on the severity of the mutation (Clifton-Bligh et al., 1998; Castanet et al., 2002; Baris et al., 2006). In vitro studies showed the complete lack of DNA binding and transcriptional activity of A65V (Clifton-Bligh et al., 1998) and R102C (Baris et al., 2006), and the partial preservation of function with the S57N (Castanet et al., 2002) mutant FOXE1 proteins, respectively.

Non-syndromic cleft lip with or without cleft palate (NS CL/P)

Disease

Rare missense mutations in FOXE1 (A207V and D285V) have been associated with isolated clefting (Vieira et al., 2005). Fine-mapping association studies

showed genome-wide significant SNPs in or near FOXE1 region (rs3758249, rs4460498, rs1443434, rs993501) in CLP patients (Marazita et al., 2009; Moreno et al., 2009). Recently, the novel homozygous polymorphism C(-1204)G in the FOXE1 promoter region that prevented the binding of MYF-5, a myogenic regulatory factor essential for the muscle-dependent craniofacial skeletal development and the fusion of primary and secondary palate, was found in non-syndromic CP patients (Venza et al., 2009).

Premature ovarian failure (POF)

Disease

Variation in FOXE1 polyalanine length from the most frequently occurring 14 alanine allele to the 16 allele increases the risk of developing POF (Watkins et al., 2006).

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This article should be referenced as such:

Venza I, Visalli M, Teti D, Venza M. FOXE1 (forkhead box E1 (thyroid transcription factor 2)). Atlas Genet Cytogenet Oncol Haematol. 2011; 15(2):183-186.