Gene Section
Review

NKX2-1 (NK2 homeobox 1)

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Identity

**Other names: BCH, BHC, NK-2, NKX2.1, NKX2A,
TEBP, TITF1, TTF-1, TTF1**
HGNC (Hugo): NKX2-1
Location: 14q13.3

DNA/RNA

Description

NKX2-1 is regulated by two promoter regions: the first one is located in intron 1 (5' of exon 1, regulation of NKX2-1 in lung and thyroid cells).

The second one is situated in the 5' flanking region of exon 1, it is a 330 bp TATA-less region containing multiple palindromes and G/C-rich elements. It regulates NKX2-1 in lung epithelial cells responding to transcription factors sp1 and sp3.

Transcription

NKX2-1 is transcribed in two highly conserved forms: mRNA-isoform 1 contains exon 1, exon 2, and exon 3, it is translated into a 401 amino acid protein and represents the minor transcript. mRNA-isoform 2 is the predominant transcript containing exon 2 and exon 3. It is translated into a 371 aa protein.
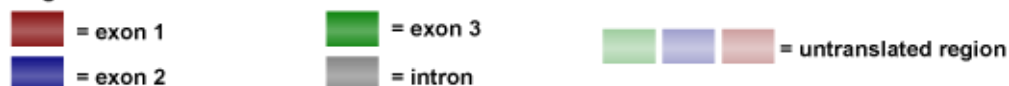

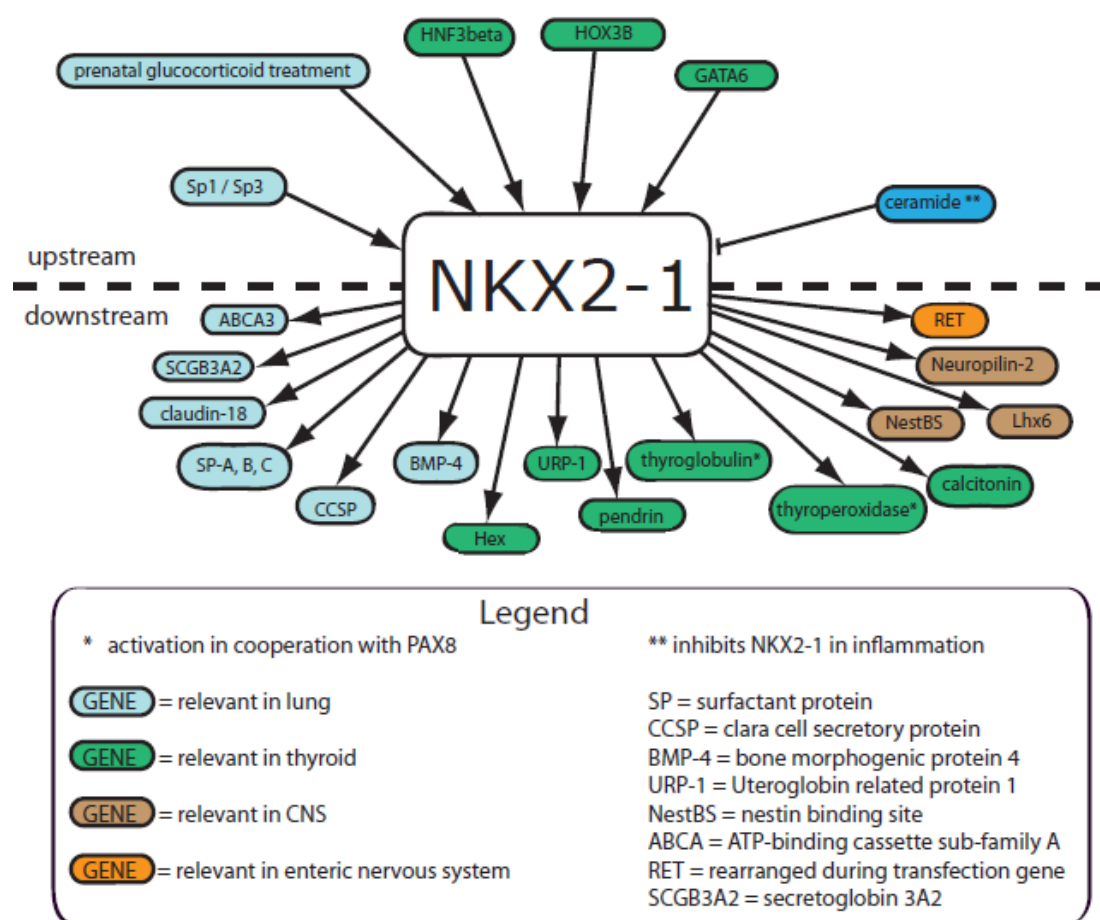**Figure 1.** NKX2-1 gene and NKX2-1 mRNA.

Figure 2. Upstream and downstream targets of NKX2-1.

Protein

Description

The NKX2-1 protein includes three functional domains: an N-terminal transactivation domain, a DNA-binding transactivation domain and a C-terminal transactivation domain.

Expression

In the lung, expression of NKX2-1 is consistent throughout all life stages from fetal to adult tissue. It is expressed in conducting airways type II alveolar epithelial cells and Clara cells and uniformly in the terminal respiratory unit.
NKX2-1 expression is also found in thyroid follicular cells and both normal and hyperplastic C cells where it activates calcitonin gene expression.
NKX2-1 is not expressed in adult neurons of the basal ganglia.
During embryonic and fetal development, NKX2-1 expression is found in various tissues (e.g. brain, lung, thyroid), for details see "function" → "Embryonic and fetal development".

Localisation

NKX2-1 is a nuclear transcription factor.

Function

In the lung, NKX2-1 regulates the expression of the lung-specific genes: surfactant protein SP-A, SP-B, SP-C and Clara cell secretory protein (CCSP).
It cooperates with C/EBPalpha in transactivating CCSP.
In the transcription of SP-C, NKX2-1 interacts with nuclear factor I to differentially regulate the transcription. The longer NKX2-1 isoform reduces transactivation of SP-C, probably due to some kind of interference.
NKX2-1 is a key activator of SP-B gene expression having at least two binding sites at the SP-B promoter and enhancer. The transactivation capacity of NKX2-1 regarding the expression of SP-B is controlled by the sphingolipid ceramide which is produced in inflammation and reduces NKX2-1 binding capacity to the SP-B promoter. SP-B transcription is also inhibited by TGFbeta1-mediated interaction of smad3 with NKX2-1. Moreover, NKX2-1 interacts with retinoic acid receptor (RAR), nuclear receptor coactivators (p160, CBP/p300) and signal transducers and activators of transcription 3 (STAT3) in regulation of SP-B expression.
Furthermore, NKX2-1 regulates the expression of the

secretoglobulin 3A2 gene (SCGB3A2) in mouse airways in cooperation with CAATT/enhancer binding proteins alpha and delta as well as the expression of ABCA3 which encodes for a lipid transporter critical for surfactant function at birth and formation of lamellar bodies.

NKX2-1 also plays an important role in the endocrine system: it regulates the expression of the thyroid-specific genes thyroglobulin, thyroid peroxidase, thyrotropin receptor and sodium-iodide-symporter, therefore being crucial for proper thyroid hormone synthesis.

Deletion of NKX2-1 in differentiated neurons of the hypothalamus in mice causes delayed puberty, reduced reproductive capacity and a shorter reproductive span in female mice, suggesting that NKX2-1 plays an important role in juvenile and adult endocrine function.

During embryonic and fetal development, NKX2-1 is active in various organs, especially lung, thyroid and brain.

As a crucial factor for lung development, NKX2-1 is expressed in the ventral foregut endoderm at a very early stage functioning as a signal which is essential for specification of a pulmonary cell fate instead of a liver cell fate. At a later stage, NKX2-1 is critical to the formation of distal pulmonary structures (whereas proximal lung differentiation is NKX2-1-independent), a function in which it is inhibited by TGF-beta.

In addition to that NKX2-1 regulates surfactant protein genes that are important for the development of alveolar stability at birth. It induces SP-A gene expression in fetal lung type II cells through increased binding of NKX2-1 (mediated by cAMP) and the NFkappa-B proteins p50 and p65. Supporting the notion of NKX2-1-dependent SP-expression, lung and associated respiratory dysfunction in neonates caused by SP-B-deficiency are partly induced by down-regulation of NKX2-1. The main therapeutical option, prenatal glucocorticoid treatment, induces the expression of NKX2-1. NKX2-1 regulates expression of uteroglobin-related protein-1 and claudin-18 during lung development.

During thyroid gland organogenesis NKX2-1 is expressed in the ultimobranchial body (UBB) and in the thyroid diverticulum. It is important for the survival of UBB-cells and eventually their dissemination into the thyroid diverticulum and for the formation of the UBB-derived vesicular structure. Pendrin and thyroglobulin are downstream targets of NKX2-1 during thyroid differentiation. The transactivational activity of NKX2-1 during thyroid development can be inhibited by NKX2-5.

In the course of brain development, NKX2-1 expression is found in both telencephalic and diencephalic domains. It cooperates with Gsh2 to pattern the ventral telencephalon. Lack of functional NKX2-1 protein in neurons impairs developmental differentiation and organization of basal ganglia and basal forebrain. NKX2-1 upregulates the transcription of nestin, an intermediate filament protein expressed in multipotent neuroepithelial cells, by direct binding to a HRE-CRE-like site (NestBS) within a CNS-specific enhancer, which indicates that nestin might be at least one of the effectors of NKX2-1 during forebrain development.

NKX2-1 expression occurs in neurons of the arcuate nucleus of the hypothalamus and in glia cells (tanycytes) in neonatal and adult mice, as well as in fetal and adult pituicytes suggesting that NKX2-1 is essential for proper development of the hypothalamus. Lack of NKX2-1 causes aberrant trajectory of the dopaminergic pathway in the developing hypothalamus (mouse-model), development of GABAergic and cholinergic neurons is also impaired in NKX2-1 defective mice. Furthermore, NKX2-1 regulates the specification of oligodendrocytes and controls the postmitotic migration of interneurons originating in the medial ganglionic eminence to either the cortex (downregulation of NKX2-1) or the striatum (maintenance of NKX2-1 expression and thus direct transcriptional activation of neuropilin-2, a guidance receptor in postmitotic cells). By directly activating Lhx6 during embryonic development NKX2-1 plays an essential role for the specification of cortical interneurons which express parvalbumin or somatostatin.

In accordance with the findings concerning the role of NKX2-1 in the development of the above-mentioned organs, NKX2-1-defective mice die at birth due to a characteristic set of malformations and functional impairments: hypoplastic lungs and insufficient surfactant production, defective hypothalamus, absence of thyroid and pituitary gland, delayed development of dopaminergic, GABAergic and cholinergic neurons.

Mutations

Note

Germinal

Mutations in NKX2-1 (for details see table 1) can cause benign hereditary chorea (BHC, a dyskinesia, i.e. a neurological disorder characterized by abnormal involuntary movements) and brain-lung-thyroid syndrome (in addition to BHC, patients suffer from congenital hypothyroidism and infant respiratory distress syndrome).

A heterozygous substitution at position 1016 in the coding sequence (C → T) leads to a mutant NKX2-1 protein (A339V) and can contribute to a predisposition for multinodular goiter and papillary thyroid carcinoma.

Brain-lung-thyroid syndrome congenital hypothyreoidism, infant respiratory distress syndrome, benign hereditary chorea			
SNP	bp 523	G → T	premature stop codon at postition 175
SNP	bp 609	C → A	premature stop codon at position 145
SNP	bp 1320	C → A	premature stop codon at position 75
SNP	bp 2626	G → T	missense mutation: valine → phenylalanine at position 14 of DNA-binding-domain
SNP	splice acceptor site of intron 2	A → T	altered mRNA structure => incorrect removal of introns
Deletion	14q11.2-q13.3		
Insertion	bp 2595		insertion of GG frameshift mutation: causes truncated protein lacking the entire third helix of the homeodomain
Cancer predisposition can contribute to predisposition for multinodular goiter and papillary thyroid carcinoma.			
SNP	bp 1016	C → T	missense mutation: A339V

Table 1. Mutations in NKX2-1 gene.

For other heterozygous NKX2-1 mutations in humans, phenotypes vary widely.

Thyroid dysfunction ranges from mild hypothyrotrophinaemia to severe congenital hypothyroidism due to thyroid hypoplasia or even agenesis. Implication of the lung ranges from a slight increase in pulmonary infections to severe neonatal respiratory distress syndrome.

Homozygous NKX2-1 mutations in humans are probably not viable.

Implicated in

Various cancers

Note

NKX2-1 expression has been found in a variety of tumor entities, especially lung and thyroid tumors (for details see table 2).

Lung neoplasms

Disease

NKX2-1 is strongly expressed in 75-90% of primary lung adenocarcinomas, whereas only 1/4 of bronchioloalveolar carcinomas show NKX2-1 positivity. Among non-small cell lung cancers, NKX2-1 is not expressed in squamous cell lung cancer.

Small cell lung cancer, as well as pulmonary carcinoids and non-neuroendocrine large-cell carcinomas partly exhibit NKX2-1 protein expression.

Prognosis

Overall, NKX2-1 expression is a predictor for better survival in adenocarcinomas of the lung (just one smaller study suggested that NKX2-1 expression is associated with poor prognosis). Controversially, NKX2-1 pathway activation in lung cancers is associated with poor survival and cisplatin resistance if PAX9 or Nkx2-8 pathways are activated at the same time.

Oncogenesis

NKX2-1 is highly amplified in 5-15% of primary lung adenocarcinomas. In cells harbouring NKX2-1 amplification, this recurrent gene amplification seems to be a mechanism of high-level NKX2-1 expression.

For a subset of lung adenocarcinomas (especially those which are derived from the terminal respiratory unit) sustained expression of NKX2-1 has been shown to be crucial for the survival of tumor cells. In these tumors RNAi inhibition of NKX2-1 induces proliferation inhibition, growth inhibition and apoptosis (lineage-specific dependency model).

Interestingly, NKX2-1 is also an activator of HOP (Hsp70/Hsp90 Organizing Protein), a potential tumor suppressor gene in lung cancer, and it inhibits EMT (epithelial to mesenchymal transition). NKX2-1 restores epithelial phenotypes in lung adenocarcinomas, acting as an adversary of the EMT-stimulating TGF-beta and a suppressor of tumor progression and invasiveness. TGF-beta inhibits the expression of NKX2-1 and thus lung morphogenesis.

Moreover, NKX2-1 is expressed in most metastatic lung adenocarcinomas.

Thyroid neoplasms

Disease

Well-differentiated thyroid follicular cell tumors, such as follicular adenomas, follicular carcinomas and papillary carcinomas exhibit strong nuclear positivity for NKX2-1 staining. In contrast, undifferentiated thyroid carcinomas show low or no immunoreaction.

	Consistently expressed	Occasionally expressed	Not expressed
Thyroid	- Papillary carcinoma - Follicular carcinoma - Medullary carcinoma - Hurthle cell carcinoma - Follicular adenoma - Hyperplastic follicular cells		- Undifferentiated thyroid carcinomas
Lung	- Adenocarcinoma - Small cell lung cancer (SCLC) - Pleural effusions of SCLC - Pulmonary sclerosing hemangioma - Bronchioloalveolar carcinoma (except for mucinous parts) - Non-neuroendocrine large-cell carcinoma - Signet-ring cell carcinomas of lung origin	- Pulmonary carcinoids (50%)	- Squamous cell lung cancer - Pleural mesothelioma - Bronchioloalveolar carcinomas (just mucinous parts) - Basaloid carcinoma of the lung
Gastrointestinal system	- Small cell cancer of the esophagus	- Colorectal carcinoma	
Genitourinary system		- Small cell carcinoma of the urine bladder - Nephroblastoma - Endometrial carcinoma - Endocervical carcinoma	
Thymus			- Thymic carcinoma - Thymoma
Skin			- Merkel cell carcinoma
Neuroectodermal		- Ependymoma - Glioblastoma	- Astrocytoma - Oligodendroglioma - Medulloblastoma - Paraganglioma - Ganglioglioma
Neuroendocrine (carcinoid tumorlets, neuroendocrine cell hyperplasia, typical carcinoids, atypical carcinoids, large cell neuroendocrine carcinomas)		- Thyroid origin - Pulmonary origin	- Thymic origin - Gastrointestinal origin - Pancreatic origin - Ovarian origin - Parathyroid adenoma - Pituitary adenoma - Pheochromocytoma
Body cavity fluids	- Lung origin (adenocarcinoma)		- Genitourinary origin - Gastrointestinal origin - Breast origin - Ovarian origin

Table 2. Expression of NKX2-1 in different tumor entities.

Concerning parafollicular cells, NKX2-1 expression can be found in normal and hyperplastic c-cells, as well as in medullary thyroid carcinomas. However, the signal intensity is much weaker and less homogenous than observed in tumors originating from follicular thyroid cells.

Non-malignant branchiogenic cysts can easily be confounded with papillary thyroid carcinomas. Since positive immunostaining for NKX2-1 has been found in a subset of these non-malignant cervical cysts, NKX2-1 cannot serve to distinguish between both entities.

Oncogenesis

NKX2-1 is expressed in most differentiated thyroid neoplasms, but not in undifferentiated tumors of thyroid origin. On DNA-level, normal thyroids and papillary carcinomas do not exhibit DNA methylation in the CpG of NKX2-1 promoter, whereas undifferenciated thyroid carcinomas show DNA methylation in this region in about 60%. Most metastases of thyroid origin are positive for NKX2-1 expression.

A heterozygous germline mutation, which leads to a mutant NKX2-1 protein has been shown to be associated with increased cell proliferation. Consequently, it might contribute to a predisposition for multinodular goiter and papillary thyroid carcinoma (for details see section mutations).

Neoplasms of the gastrointestinal tract

Disease

Small cell esophageal cancers exhibit NKX2-1 expression in the majority of cases. In contrast, carcinoids originating from the gastrointestinal tract, such as ileal, appendical, duodenal, ampullary, rectal, pancreatic and gastric carcinoids are negative for NKX2-1 immunohistochemical staining.

Neoplasms of the genitourinary tract

Disease

NKX2-1 seems to be implicated in neoplasms arising from the urinary system. Small cell carcinomas of the urinary bladder are positive for NKX2-1 staining in 25-40% of cases. Likewise, large cell neuroendocrine bladder carcinomas exhibit NKX2-1 expression. In one study, 1/6 of a set of nephroblastomas showed nuclear positivity for NKX2-1, whereas metanephric adenomas and cystic nephromas were NKX2-1 negative.

NKX2-1 expression can be found in benign tubal and endometrial epithelia, as well as in benign tumors originating from these tissues. In addition, malignant tumors of the female genital tract, such as endocervical adenocarcinomas, small cell carcinomas of the uterine cervix, endometrioid adenocarcinomas, serous carcinomas, clear cell carcinomas, and uterine malignant mixed Mullerian tumors show positivity for NKX2-1. Staining morphology in these tumors differs from rare positive cells to a diffusely positive staining pattern.

Prognosis

No correlation could be detected between positive NKX2-1 immunostaining in small cell carcinomas of the urinary bladder and clinicopathologic features (including outcome, age, sex, smoking history, stage and metastatic status).

Neuroendocrine neoplasms

Disease

Among well-differentiated neuroendocrine tumors, only those tumors originating from the lung or thyroid are positive for NKX2-1 expression. Neither gastrointestinal typical or atypical carcinoids, nor neuroendocrine tumors from other sites (e.g. Merkel cell carcinomas, thymic carcinoids, ovarian large cell neuroendocrine carcinomas) show NKX2-1 expression. Concerning small cell carcinomas, NKX2-1 expression is not specific for small cell lung cancer, as NKX2-1 expression can also be found in small cell carcinomas originating from the esophagus, prostate, bladder or uterine cervix.

Neoplasms of neuroectodermal origin

Disease

NKX2-1 occasionally has been detected in glioblastoma multiforme and in ependymomas of the third ventricle. Other primary brain tumors, such as astrocytomas, oligodendrogliomas, medulloblastomas and gangliomas from various sites do not exhibit NKX2-1 expression.

Sellar tumors, including pituicytomas, atypical pituicytomas, granular cell tumors and spindle cell oncocytomas can show positive immunostaining for NKX2-1.

To be noted

Note

NKX2-1 has been well studied in neoplasms of the lung and thyroid, but lacks a sufficient level of evidence in other tumor entities.

References

Kimura S, Hara Y, Pineau T, Fernandez-Salguero P, Fox CH, Ward JM, Gonzalez FJ. The T/ebp null mouse: thyroid-specific enhancer-binding protein is essential for the organogenesis of the thyroid, lung, ventral forebrain, and pituitary. Genes Dev. 1996 Jan 1;10(1):60-9

Whitsett JA, Glasser SW. Regulation of surfactant protein gene transcription. Biochim Biophys Acta. 1998 Nov 19;1408(2-3):303-11

Agoff SN, Lamps LW, Philip AT, Amin MB, Schmidt RA, True LD, Folpe AL. Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. Mod Pathol. 2000 Mar;13(3):238-42

Katoh R, Kawaoi A, Miyagi E, Li X, Suzuki K, Nakamura Y, Kakudo K. Thyroid transcription factor-1 in normal, hyperplastic, and neoplastic follicular thyroid cells examined by immunohistochemistry and nonradioactive in situ hybridization. Mod Pathol. 2000 May;13(5):570-6

Katoh R, Miyagi E, Nakamura N, Li X, Suzuki K, Kakudo K, Kobayashi M, Kawaoi A. Expression of thyroid transcription factor-1 (TTF-1) in human C cells and medullary thyroid carcinomas. Hum Pathol. 2000 Mar;31(3):386-93

Li C, Cai J, Pan Q, Minoo P. Two functionally distinct forms of NKX2.1 protein are expressed in the pulmonary epithelium. Biochem Biophys Res Commun. 2000 Apr 13;270(2):462-8

Li C, Ling X, Yuan B, Minoo P. A novel DNA element mediates transcription of Nkx2.1 by Sp1 and Sp3 in pulmonary epithelial cells. Biochim Biophys Acta. 2000 Feb 29;1490(3):213-24

Losada A, Tovar JA, Xia HM, Diez-Pardo JA, Santisteban P. Down-regulation of thyroid transcription factor-1 gene expression in fetal lung hypoplasia is restored by glucocorticoids. Endocrinology. 2000 Jun;141(6):2166-73

Yuan B, Li C, Kimura S, Engelhardt RT, Smith BR, Minoo P. Inhibition of distal lung morphogenesis in Nkx2.1(-/-) embryos. Dev Dyn. 2000 Feb;217(2):180-90

Cheuk W, Kwan MY, Suster S, Chan JK. Immunostaining for thyroid transcription factor 1 and cytokeratin 20 aids the distinction of small cell carcinoma from Merkel cell carcinoma, but not pulmonary from extrapulmonary small cell carcinomas. Arch Pathol Lab Med. 2001 Feb;125(2):228-31

Jang KY, Kang MJ, Lee DG, Chung MJ. Utility of thyroid transcription factor-1 and cytokeratin 7 and 20 immunostaining in the identification of origin in malignant effusions. Anal Quant Cytol Histol. 2001 Dec;23(6):400-4

Merchant SH, Amin MB, Tamboli P, Ro J, Ordóñez NG, Ayala AG, Czerniak BA, Ro JY. Primary signet-ring cell carcinoma of lung: immunohistochemical study and comparison with non-pulmonary signet-ring cell carcinomas. Am J Surg Pathol. 2001 Dec;25(12):1515-9

Niimi T, Keck-Waggoner CL, Popescu NC, Zhou Y, Levitt RC, Kimura S. UGRP1, a uteroglobin/Clara cell secretory protein-related protein, is a novel lung-enriched downstream target gene for the T/EBP/NKX2.1 homeodomain transcription factor. Mol Endocrinol. 2001 Nov;15(11):2021-36

Niimi T, Nagashima K, Ward JM, Minoo P, Zimonjic DB, Popescu NC, Kimura S. claudin-18, a novel downstream target gene for the T/EBP/NKX2.1 homeodomain transcription factor, encodes lung- and stomach-specific isoforms through alternative splicing. Mol Cell Biol. 2001 Nov;21(21):7380-90

Oliveira AM, Tazelaar HD, Myers JL, Erickson LA, Lloyd RV. Thyroid transcription factor-1 distinguishes metastatic pulmonary from well-differentiated neuroendocrine tumors of other sites. Am J Surg Pathol. 2001 Jun;25(6):815-9

Puglisi F, Aprile G, Bruckbauer M, Barbone F, Damante G, Guerra S, Beltrami CA, Di Loreto C. Combined analysis of MIB-1 and thyroid transcription factor-1 predicts survival in non-small cell lung carcinomas. Cancer Lett. 2001 Jan 10;162(1):97-103

Sturm N, Lantuéjoul S, Laverrière MH, Papotti M, Brichon PY, Brambilla C, Brambilla E. Thyroid transcription factor 1 and cytokeratins 1, 5, 10, 14 (34betaE12) expression in basaloid and large-cell neuroendocrine carcinomas of the lung. Hum Pathol. 2001 Sep;32(9):918-25

Cassel TN, Berg T, Suske G, Nord M. Synergistic transactivation of the differentiation-dependent lung gene Clara cell secretory protein (secretoglobin 1a1) by the basic region leucine zipper factor CCAAT/enhancer-binding protein alpha and the homeodomain factor Nkx2.1/thyroid transcription factor-1. J Biol Chem. 2002 Oct 4;277(40):36970-7

Gomez-Fernandez C, Jorda M, Delgado PI, Ganjei-Azar P. Thyroid transcription factor 1: a marker for lung adenoarinoma in body cavity fluids. Cancer. 2002 Oct 25;96(5):289-93

Krude H, Schütz B, Biebermann H, von Moers A, Schnabel D, Neitzel H, Tönnies H, Weise D, Lafferty A, Schwarz S, DeFelice M, von Deimling A, van Landeghem F, DiLauro R, Grüters A. Choreoathetosis, hypothyroidism, and pulmonary alterations due to human NKX2-1 haploinsufficiency. J Clin Invest. 2002 Feb;109(4):475-80

Lau SK, Desrochers MJ, Luthringer DJ. Expression of thyroid transcription factor-1, cytokeratin 7, and cytokeratin 20 in bronchioloalveolar carcinomas: an immunohistochemical evaluation of 67 cases. Mod Pathol. 2002 May;15(5):538-42

Lin D, Zou S, Lu N, Liu X, Wen P, Li L. Thyroid transcription factor-1 in the histogenesis of plumonary sclerosing hemangioma. Zhonghua Zhong Liu Za Zhi. 2002 Jul;24(4):384-7

Miccadei S, De Leo R, Zammarchi E, Natali PG, Civitareale D. The synergistic activity of thyroid transcription factor 1 and Pax 8 relies on the promoter/enhancer interplay. Mol Endocrinol. 2002 Apr;16(4):837-46

Tamiolakis D, Papadopoulos N, Cheva A, Lambropoulou M, Kotini A, Mikroulis D, Didilis V, Bitzikas N, Bougioukas G. Immunocytochemical profile of malignant pleural effusions of small-cell lung cancer. Minerva Med. 2002 Dec;93(6):479-83

Yatabe Y, Mitsudomi T, Takahashi T. TTF-1 expression in pulmonary adenocarcinomas. Am J Surg Pathol. 2002 Jun;26(6):767-73

Zamecnik J, Kodet R. Value of thyroid transcription factor-1 and surfactant apoprotein A in the differential diagnosis of pulmonary carcinomas: a study of 109 cases. Virchows Arch. 2002 Apr;440(4):353-61

Bachurski CJ, Yang GH, Currier TA, Gronostajski RM, Hong D. Nuclear factor I/thyroid transcription factor 1 interactions modulate surfactant protein C transcription. Mol Cell Biol. 2003 Dec;23(24):9014-24

Corbin JG, Rutlin M, Gaiano N, Fishell G. Combinatorial function of the homeodomain proteins Nkx2.1 and Gsh2 in ventral telencephalic patterning. Development. 2003 Oct;130(20):4895-906

Kawano H, Horie M, Honma S, Kawamura K, Takeuchi K, Kimura S. Aberrant trajectory of ascending dopaminergic pathway in mice lacking Nkx2.1. Exp Neurol. 2003 Jul;182(1):103-12

Kleiner-Fisman G, Rogaeva E, Halliday W, Houle S, Kawarai T, Sato C, Medeiros H, St George-Hyslop PH, Lang AE. Benign hereditary chorea: clinical, genetic, and pathological findings. Ann Neurol. 2003 Aug;54(2):244-7

Pan CC, Chen PC, Chou TY, Chiang H. Expression of calretinin and other mesothelioma-related markers in thymic carcinoma and thymoma. Hum Pathol. 2003 Nov;34(11):1155-62

Puppin C, D'Elia AV, Pellizzari L, Russo D, Arturi F, Presta I, Filetti S, Bogue CW, Denson LA, Damante G. Thyroid-specific transcription factors control Hex promoter activity. Nucleic Acids Res. 2003 Apr 1;31(7):1845-52

Tan D, Li Q, Deeb G, Ramnath N, Slocum HK, Brooks J, Cheney R, Wiseman S, Anderson T, Loewen G. Thyroid transcription factor-1 expression prevalence and its clinical implications in non-small cell lung cancer: a high-throughput tissue microarray and immunohistochemistry study. Hum Pathol. 2003 Jun;34(6):597-604

Alcorn JL, Islam KN, Young PP, Mendelson CR. Glucocorticoid inhibition of SP-A gene expression in lung type II cells is mediated via the TTF-1-binding element. Am J Physiol Lung Cell Mol Physiol. 2004 Apr;286(4):L767-76

Bakir K, Koçer NE, Deniz H, Güldür ME. TTF-1 and surfactant-B as co-adjuvants in the diagnosis of lung adenocarcinoma and pleural mesothelioma. Ann Diagn Pathol. 2004 Dec;8(6):337-41

Du EZ, Goldstraw P, Zacharias J, Tiffet O, Craig PJ, Nicholson AG, Weidner N, Yi ES. TTF-1 expression is specific for lung primary in typical and atypical carcinoids: TTF-1-positive carcinoids are predominantly in peripheral location. Hum Pathol. 2004 Jul;35(7):825-31

Grüters A, Krude H, Biebermann H. Molecular genetic defects in congenital hypothyroidism. Eur J Endocrinol. 2004 Nov;151 Suppl 3:U39-44

Kang Y, Hebron H, Ozbun L, Mariano J, Minoo P, Jakowlew SB. Nkx2.1 transcription factor in lung cells and a transforming growth factor-beta1 heterozygous mouse model of lung carcinogenesis. Mol Carcinog. 2004 Aug;40(4):212-31

Moldvay J, Jackel M, Bogos K, Soltész I, Agócs L, Kovács G, Schaff Z. The role of TTF-1 in differentiating primary and metastatic lung adenocarcinomas. Pathol Oncol Res. 2004;10(2):85-8

Nasonkin IO, Ward RD, Raetzman LT, Seasholtz AF, Saunders TL, Gillespie PJ, Camper SA. Pituitary hypoplasia and respiratory distress syndrome in Prop1 knockout mice. Hum Mol Genet. 2004 Nov 15;13(22):2727-35

Saad RS, Liu YL, Han H, Landreneau RJ, Silverman JF. Prognostic significance of thyroid transcription factor-1 expression in both early-stage conventional adenocarcinoma and bronchioloalveolar carcinoma of the lung. Hum Pathol. 2004 Jan;35(1):3-7

Srisodsai A, Kurotani R, Chiba Y, Sheikh F, Young HA, Donnelly RP, Kimura S. Interleukin-10 induces uteroglobin-related protein (UGRP) 1 gene expression in lung epithelial cells through homeodomain transcription factor T/EBP/NKX2.1. J Biol Chem. 2004 Dec 24;279(52):54358-68

Zamecnik J, Chanova M, Kodet R. Expression of thyroid transcription factor 1 in primary brain tumours. J Clin Pathol. 2004 Oct;57(10):1111-3

Zhu NL, Li C, Xiao J, Minoo P. NKX2.1 regulates transcription of the gene for human bone morphogenetic protein-4 in lung epithelial cells. Gene. 2004 Feb 18;327(1):25-36

Asmus F, Horber V, Pohlenz J, Schwabe D, Zimprich A, Munz M, Schöning M, Gasser T. A novel TITF-1 mutation causes benign hereditary chorea with response to levodopa. Neurology. 2005 Jun 14;64(11):1952-4

Castanet M, Sura-Trueba S, Chauty A, Carré A, de Roux N, Heath S, Léger J, Lyonnet S, Czernichow P, Polak M. Linkage and mutational analysis of familial thyroid dysgenesis demonstrate genetic heterogeneity implicating novel genes. Eur J Hum Genet. 2005 Feb;13(2):232-9

Choi YL, Kim MK, Suh JW, Han J, Kim JH, Yang JH, Nam SJ. Immunoexpression of HBME-1, high molecular weight cytokeratin, cytokeratin 19, thyroid transcription factor-1, and E-cadherin in thyroid carcinomas. J Korean Med Sci. 2005 Oct;20(5):853-9

Dentice M, Luongo C, Elefante A, Ambrosio R, Salzano S, Zannini M, Nitsch R, Di Lauro R, Rossi G, Fenzi G, Salvatore D. Pendrin is a novel in vivo downstream target gene of the TTF-1/Nkx-2.1 homeodomain transcription factor in differentiated thyroid cells. Mol Cell Biol. 2005 Nov;25(22):10171-82

Grasberger H, Ringkananont U, Lefrancois P, Abramowicz M, Vassart G, Refetoff S. Thyroid transcription factor 1 rescues PAX8/p300 synergism impaired by a natural PAX8 paired

domain mutation with dominant negative activity. Mol Endocrinol. 2005 Jul;19(7):1779-91

Jones TD, Kernek KM, Yang XJ, Lopez-Beltran A, MacLennan GT, Eble JN, Lin H, Pan CX, Tretiakova M, Baldridge LA, Cheng L. Thyroid transcription factor 1 expression in small cell carcinoma of the urinary bladder: an immunohistochemical profile of 44 cases. Hum Pathol. 2005 Jul;36(7):718-23

Kreft A, Hansen T, Kirkpatrick CJ. Thyroid transcription factor 1 expression in cystic lesions of the neck: an immunohistochemical investigation of thyroglossal duct cysts, branchial cleft cysts and metastatic papillary thyroid cancer. Virchows Arch. 2005 Jul;447(1):9-11

Kumar VH, Lakshminrusimha S, El Abiad MT, Chess PR, Ryan RM. Growth factors in lung development. Adv Clin Chem. 2005;40:261-316

Marcucio RS, Cordero DR, Hu D, Helms JA. Molecular interactions coordinating the development of the forebrain and face. Dev Biol. 2005 Aug 1;284(1):48-61

Saqi A, Alexis D, Remotti F, Bhagat G. Usefulness of CDX2 and TTF-1 in differentiating gastrointestinal from pulmonary carcinoids. Am J Clin Pathol. 2005 Mar;123(3):394-404

Serls AE, Doherty S, Parvatiyar P, Wells JM, Deutsch GH. Different thresholds of fibroblast growth factors pattern the ventral foregut into liver and lung. Development. 2005 Jan;132(1):35-47

Wu M, Szporn AH, Zhang D, Wasserman P, Gan L, Miller L, Burstein DE. Cytology applications of p63 and TTF-1 immunostaining in differential diagnosis of lung cancers. Diagn Cytopathol. 2005 Oct;33(4):223-7

Berghmans T, Paesmans M, Mascaux C, Martin B, Meert AP, Haller A, Lafitte JJ, Sculier JP. Thyroid transcription factor 1--a new prognostic factor in lung cancer: a meta-analysis. Ann Oncol. 2006 Nov;17(11):1673-6

Kusakabe T, Hoshi N, Kimura S. Origin of the ultimobranchial body cyst: T/ebp/Nkx2.1 expression is required for development and fusion of the ultimobranchial body to the thyroid. Dev Dyn. 2006 May;235(5):1300-9

Kusakabe T, Kawaguchi A, Hoshi N, Kawaguchi R, Hoshi S, Kimura S. Thyroid-specific enhancer-binding protein/NKX2.1 is required for the maintenance of ordered architecture and function of the differentiated thyroid. Mol Endocrinol. 2006 Aug;20(8):1796-809

Mastronardi C, Smiley GG, Raber J, Kusakabe T, Kawaguchi A, Matagne V, Dietzel A, Heger S, Mungenast AE, Cabrera R, Kimura S, Ojeda SR. Deletion of the Ttf1 gene in differentiated neurons disrupts female reproduction without impairing basal ganglia function. J Neurosci. 2006 Dec 20;26(51):13167-79

Sparkman L, Chandru H, Boggaram V. Ceramide decreases surfactant protein B gene expression via downregulation of TTF-1 DNA binding activity. Am J Physiol Lung Cell Mol Physiol. 2006 Feb;290(2):L351-8

Tsuta K, Ishii G, Nitadori J, Murata Y, Kodama T, Nagai K, Ochiai A. Comparison of the immunophenotypes of signet-ring cell carcinoma, solid adenocarcinoma with mucin production, and mucinous bronchioloalveolar carcinoma of the lung characterized by the presence of cytoplasmic mucin. J Pathol. 2006 May;209(1):78-87

Alijo Serrano F, Sánchez-Mora N, Angel Arranz J, Hernández C, Alvarez-Fernández E. Large cell and small cell neuroendocrine bladder carcinoma: immunohistochemical and outcome study in a single institution. Am J Clin Pathol. 2007 Nov;128(5):733-9

Besnard V, Xu Y, Whitsett JA. Sterol response element binding protein and thyroid transcription factor-1 (Nkx2.1) regulate Abca3 gene expression. Am J Physiol Lung Cell Mol Physiol. 2007 Dec;293(6):L1395-405

Chen Y, Pacyna-Gengelbach M, Deutschmann N, Niesporek S, Petersen I. Homeobox gene HOP has a potential tumor suppressive activity in human lung cancer. Int J Cancer. 2007 Sep 1;121(5):1021-7

Galloway M, Sim R. TTF-1 staining in glioblastoma multiforme. Virchows Arch. 2007 Jul;451(1):109-11

Kendall J, Liu Q, Bakleh A, Krasnitz A, Nguyen KC, Lakshmi B, Gerald WL, Powers S, Mu D. Oncogenic cooperation and coamplification of developmental transcription factor genes in lung cancer. Proc Natl Acad Sci U S A. 2007 Oct 16;104(42):16663-8

Kolla V, Gonzales LW, Gonzales J, Wang P, Angampalli S, Feinstein SI, Ballard PL. Thyroid transcription factor in differentiating type II cells: regulation, isoforms, and target genes. Am J Respir Cell Mol Biol. 2007 Feb;36(2):213-25

Lin X, Saad RS, Luckasevic TM, Silverman JF, Liu Y. Diagnostic value of CDX-2 and TTF-1 expressions in separating metastatic neuroendocrine neoplasms of unknown origin. Appl Immunohistochem Mol Morphol. 2007 Dec;15(4):407-14

Siami K, McCluggage WG, Ordonez NG, Euscher ED, Malpica A, Sneige N, Silva EG, Deavers MT. Thyroid transcription factor-1 expression in endometrial and endocervical adenocarcinomas. Am J Surg Pathol. 2007 Nov;31(11):1759-63

Suzuki M, Katagiri N, Ueda M, Tanaka S. Functional analysis of Nkx2.1 and Pax9 for calcitonin gene transcription. Gen Comp Endocrinol. 2007 Jun-Jul;152(2-3):259-66

Tanaka H, Yanagisawa K, Shinjo K, Taguchi A, Maeno K, Tomida S, Shimada Y, Osada H, Kosaka T, Matsubara H, Mitsudomi T, Sekido Y, Tanimoto M, Yatabe Y, Takahashi T. Lineage-specific dependency of lung adenocarcinomas on the lung development regulator TTF-1. Cancer Res. 2007 Jul 1;67(13):6007-11

Weir BA, Woo MS, Getz G, Perner S, Ding L, Beroukhim R, Lin WM, Province MA, Kraja A, Johnson LA, Shah K, Sato M, Thomas RK, Barletta JA, Borecki IB, Broderick S, Chang AC, Chiang DY, Chirieac LR, Cho J, Fujii Y, Gazdar AF, Giordano T, Greulich H, Hanna M, Johnson BE, Kris MG, Lash A, Lin L, Lindeman N, Mardis ER, McPherson JD, Minna JD, Morgan MB, Nadel M, Orringer MB, Osborne JR, Ozenberger B, Ramos AH, Robinson J, Roth JA, Rusch V, Sasaki H, Shepherd F, Sougnez C, Spitz MR, Tsao MS, Twomey D, Verhaak RG, Weinstock GM, Wheeler DA, Winckler W, Yoshizawa A, Yu S, Zakowski MF, Zhang Q, Beer DG, Wistuba II, Watson MA, Garraway LA, Ladanyi M, Travis WD, Pao W, Rubin MA, Gabriel SB, Gibbs RA, Varmus HE, Wilson RK, Lander ES, Meyerson M. Characterizing the cancer genome in lung adenocarcinoma. Nature. 2007 Dec 6;450(7171):893-8

Yun JP, Zhang MF, Hou JH, Tian QH, Fu J, Liang XM, Wu QL, Rong TH. Primary small cell carcinoma of the esophagus: clinicopathological and immunohistochemical features of 21 cases. BMC Cancer. 2007 Mar 3;7:38

Zhang Y, Rath N, Hannenhalli S, Wang Z, Cappola T, Kimura S, Atochina-Vasserman E, Lu MM, Beers MF, Morrisey EE. GATA and Nkx factors synergistically regulate tissue-specific gene expression and development in vivo. Development. 2007 Jan;134(1):189-98

Akagi T, Luong QT, Gui D, Said J, Selektar J, Yung A, Bunce CM, Braunstein GD, Koeffler HP. Induction of sodium iodide symporter gene and molecular characterisation of HNF3

beta/FoxA2, TTF-1 and C/EBP beta in thyroid carcinoma cells. Br J Cancer. 2008 Sep 2;99(5):781-8

Butt SJ, Sousa VH, Fuccillo MV, Hjerling-Leffler J, Miyoshi G, Kimura S, Fishell G. The requirement of Nkx2-1 in the temporal specification of cortical interneuron subtypes. Neuron. 2008 Sep 11;59(5):722-32

Chuang WY, Yeh CJ, Chu PH, Liao CC, Wu CT, Chuang CC, Pai PC, Tseng CK, Jung SM, Wei KC, Chang CN. Expression of thyroid transcription factor-1 in brain metastases: a useful indicator of pulmonary origin. J Clin Neurosci. 2008 Jun;15(6):643-6

Du T, Xu Q, Ocbina PJ, Anderson SA. NKX2.1 specifies cortical interneuron fate by activating Lhx6. Development. 2008 Apr;135(8):1559-67

Ferrara AM, De Michele G, Salvatore E, Di Maio L, Zampella E, Capuano S, Del Prete G, Rossi G, Fenzi G, Filla A, Macchia PE. A novel NKX2.1 mutation in a family with hypothyroidism and benign hereditary chorea. Thyroid. 2008 Sep;18(9):1005-9

Kubba LA, McCluggage WG, Liu J, Malpica A, Euscher ED, Silva EG, Deavers MT. Thyroid transcription factor-1 expression in ovarian epithelial neoplasms. Mod Pathol. 2008 Apr;21(4):485-90

Kwei KA, Kim YH, Girard L, Kao J, Pacyna-Gengelbach M, Salari K, Lee J, Choi YL, Sato M, Wang P, Hernandez-Boussard T, Gazdar AF, Petersen I, Minna JD, Pollack JR. Genomic profiling identifies TITF1 as a lineage-specific oncogene amplified in lung cancer. Oncogene. 2008 Jun 5;27(25):3635-40

Lin JD. Thyroglobulin and human thyroid cancer. Clin Chim Acta. 2008 Feb;388(1-2):15-21

Maeshima AM, Omatsu M, Tsuta K, Asamura H, Matsuno Y. Immunohistochemical expression of TTF-1 in various cytological subtypes of primary lung adenocarcinoma, with special reference to intratumoral heterogeneity. Pathol Int. 2008 Jan;58(1):31-7

Nóbrega-Pereira S, Kessaris N, Du T, Kimura S, Anderson SA, Marín O. Postmitotic Nkx2-1 controls the migration of telencephalic interneurons by direct repression of guidance receptors. Neuron. 2008 Sep 11;59(5):733-45

Pelizzoli R, Tacchetti C, Luzzi P, Strangio A, Bellese G, Zappia E, Guazzi S. TTF-1/NKX2.1 up-regulates the in vivo transcription of nestin. Int J Dev Biol. 2008;52(1):55-62

Perner S, Wagner PL, Demichelis F, Mehra R, Lafargue CJ, Moss BJ, Arbogast S, Soltermann A, Weder W, Giordano TJ, Beer DG, Rickman DS, Chinnaiyan AM, Moch H, Rubin MA. EML4-ALK fusion lung cancer: a rare acquired event. Neoplasia. 2008 Mar;10(3):298-302

Tomita T, Kido T, Kurotani R, Iemura S, Sterneck E, Natsume T, Vinson C, Kimura S. CAATT/enhancer-binding proteins alpha and delta interact with NKX2-1 to synergistically activate mouse secretoglobin 3A2 gene expression. J Biol Chem. 2008 Sep 12;283(37):25617-27

van den Akker WM, Brox A, Puelles L, Durston AJ, Medina L. Comparative functional analysis provides evidence for a crucial role for the homeobox gene Nkx2.1/Titf-1 in forebrain evolution. J Comp Neurol. 2008 Jan 10;506(2):211-23

Xing Y, Li C, Hu L, Tiozzo C, Li M, Chai Y, Bellusci S, Anderson S, Minoo P. Mechanisms of TGFbeta inhibition of LUNG endodermal morphogenesis: the role of TbetaRII, Smads, Nkx2.1 and Pten. Dev Biol. 2008 Aug 15;320(2):340-50

Bisceglia M, Ragazzi M, Galliani CA, Lastilla G, Rosai J. TTF-1 expression in nephroblastoma. Am J Surg Pathol. 2009 Mar;33(3):454-61

Carré A, Szinnai G, Castanet M, Sura-Trueba S, Tron E, Broutin-L'Hermite I, Barat P, Goizet C, Lacombe D, Moutard ML, Raybaud C, Raynaud-Ravni C, Romana S, Ythier H, Léger J, Polak M. Five new TTF1/NKX2.1 mutations in brain-lung-thyroid syndrome: rescue by PAX8 synergism in one case. Hum Mol Genet. 2009 Jun 15;18(12):2266-76

Fazzari P. Transcription factors make a turn into migration. Cell Adh Migr. 2009 Jan-Mar;3(1):1-2

Hoshi S, Hoshi N, Okamoto M, Paiz J, Kusakabe T, Ward JM, Kimura S. Role of NKX2-1 in N-bis(2-hydroxypropyl)-nitrosamine-induced thyroid adenoma in mice. Carcinogenesis. 2009 Sep;30(9):1614-9

Hsu DS, Acharya CR, Balakumaran BS, Riedel RF, Kim MK, Stevenson M, Tuchman S, Mukherjee S, Barry W, Dressman HK, Nevins JR, Powers S, Mu D, Potti A. Characterizing the developmental pathways TTF-1, NKX2-8, and PAX9 in lung cancer. Proc Natl Acad Sci U S A. 2009 Mar 31;106(13):5312-7

Kondo T, Nakazawa T, Ma D, Niu D, Mochizuki K, Kawasaki T, Nakamura N, Yamane T, Kobayashi M, Katoh R. Epigenetic silencing of TTF-1/NKX2-1 through DNA hypermethylation and histone H3 modulation in thyroid carcinomas. Lab Invest. 2009 Jul;89(7):791-9

Lee EB, Tihan T, Scheithauer BW, Zhang PJ, Gonatas NK. Thyroid transcription factor 1 expression in sellar tumors: a histogenetic marker? J Neuropathol Exp Neurol. 2009 May;68(5):482-8

Ngan ES, Lang BH, Liu T, Shum CK, So MT, Lau DK, Leon TY, Cherny SS, Tsai SY, Lo CY, Khoo US, Tam PK, Garcia-Barceló MM. A germline mutation (A339V) in thyroid transcription factor-1 (TITF-1/NKX2.1) in patients with multinodular goiter and papillary thyroid carcinoma. J Natl Cancer Inst. 2009 Feb 4;101(3):162-75

Perner S, Wagner PL, Soltermann A, LaFargue C, Tischler V, Weir BA, Weder W, Meyerson M, Giordano TJ, Moch H, Rubin MA. TTF1 expression in non-small cell lung carcinoma: association with TTF1 gene amplification and improved survival. J Pathol. 2009 Jan;217(1):65-72

Saito RA, Watabe T, Horiguchi K, Kohyama T, Saitoh M, Nagase T, Miyazono K. Thyroid transcription factor-1 inhibits transforming growth factor-beta-mediated epithelial-to-mesenchymal transition in lung adenocarcinoma cells. Cancer Res. 2009 Apr 1;69(7):2783-91

Strojan Flezar M, Srebotnik Kirbis I. Identification of carcinoma origin by thyroid transcription factor-1 immunostaining of fine needle aspirates of metastases. Cytopathology. 2009 Jun;20(3):176-82

Yee CL, Wang Y, Anderson S, Ekker M, Rubenstein JL. Arcuate nucleus expression of NKX2.1 and DLX and lineages expressing these transcription factors in neuropeptide Y(+), proopiomelanocortin(+), and tyrosine hydroxylase(+) neurons in neonatal and adult mice. J Comp Neurol. 2009 Nov 1;517(1):37-50

Zhang PJ, Gao HG, Pasha TL, Litzky L, Livolsi VA. TTF-1 expression in ovarian and uterine epithelial neoplasia and its potential significance, an immunohistochemical assessment with multiple monoclonal antibodies and different secondary detection systems. Int J Gynecol Pathol. 2009 Jan;28(1):10-8

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