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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.

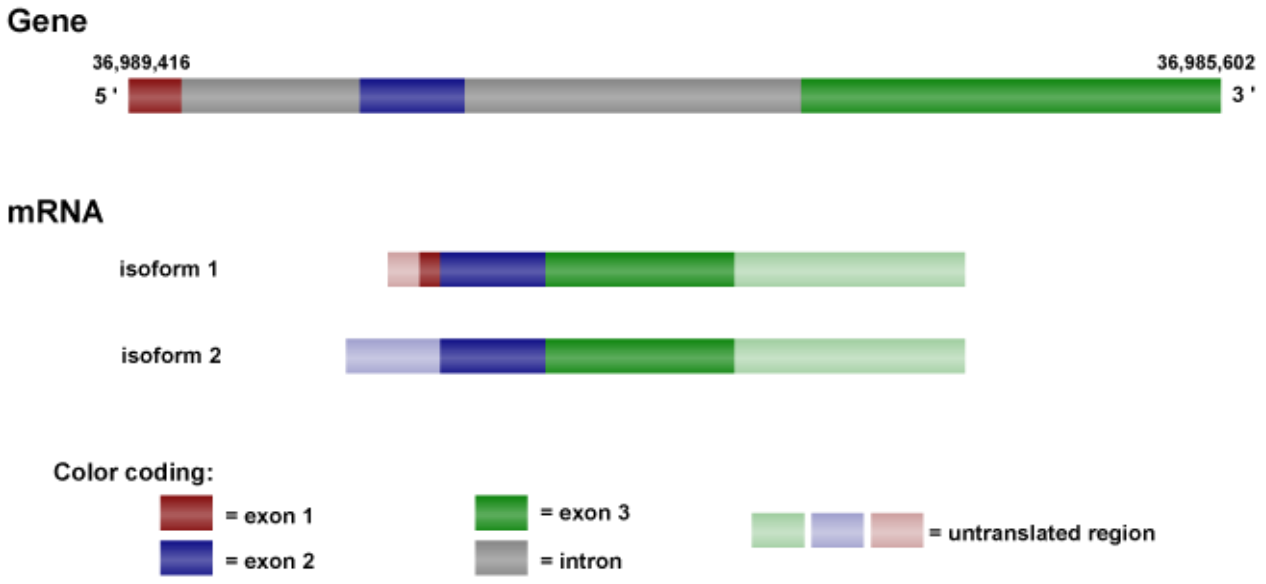

Figure 1. NKX2-1 gene and NKX2-1 mRNA.

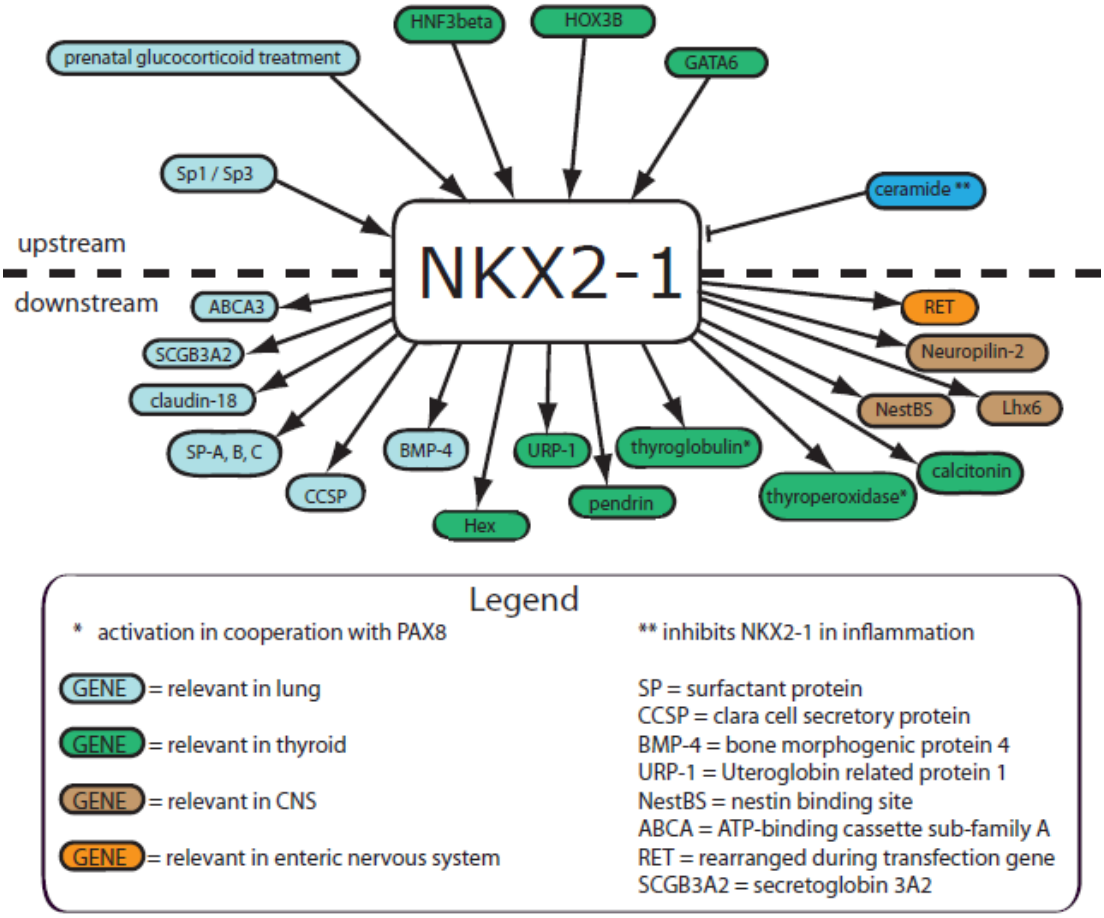

Figure 2. Upstream and downstream targets of NKX2-1.

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.

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