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Gene Section
Review

PAX8 (paired box 8)

Dario de Biase, Luca Morandi, Giovanni Tallini

Bologna University School of Medicine, Anatomia Patologica, Ospedale Bellaria, Via Altura 3, 40139 Bologna, Italy (DdB, LM, GT)

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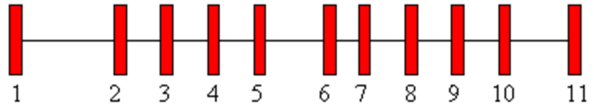
Identity

HGNC (Hugo): PAX8

Location: 2q13

DNA/RNA



Structure of PAX8 gene.

Description

62924 bp, 11 exons, cDNA 4065 bp.

Transcription

Five different isoforms due to alternative splicing.

Protein

Description

Pax8 is a transcription factor. The molecular weight of the unprocessed precursor is ~48 kD. Five different isoforms have been described (a-e):

-Isoform a (450 aa, 4065 bp)

-Isoform b (387 aa, 3876 bp, lack exon 8; mass of ~42 kD)

-Isoform c (398 aa, 3986 bp, lack exons 7, 8; mass of ~43 kD)

-Isoform d (321 aa, 3755 bp, lack exon 8; mass of ~35 kD)

-Isoform e (287 aa, 3653 bp, lack exons 8, 9, 10; mass of ~31 kD)

Expression

Pax8 is expressed in embryonal human tissues, in particular in the developing thyroid gland, kidney,

Müllerian structures, and nervous system (e.g. otic placode), and in the human placenta. During thyroid development PAX8 is expressed in the thyroid anlage. During kidney development it is expressed in the S-shaped body and in the early proximal tube, but is absent in the uretic bud and condensing mesenchyme. In the adult Pax8 is expressed in the thyroid gland and kidney but it is absent in most other developed organs. Pax8 expression has been described in several tumor types including thyroid and ovarian carcinomas and Wilms' tumor.

Localisation

Cell nucleus.

Function

The paired box (PAX) genes code for a family of transcription factors containing a paired box domain, an octapeptide, and a paired-type homeo-domain. PAX proteins are essential for the forma-tion of several tissues from all germ layers in the mammalian embryo. Pax8 is a member of this family with a crucial role in the morphogenesis of the thyroid gland. It also has an important organogenetic role for the kidney, Müllerian system and inner ear.

In the thyroid, Pax8 is a master gene that regulates maintenance of the differentiated thyroid follicular cell phenotype. As such it controls and activates the transcription and thyroid specific expression of the main proteins responsible for the functional activity of follicular cells such as TG (thyroglobulin), TPO

(thyroperoxidase) and NIS (sodium/iodide symporter).

In the developing Kidney PAX8 is important for renal vescicle formation and regulates the expression of the WT1 gene.

Homology

PAX family members (especially PAX2).

Mutations

Note

Germ line PAX8 mutations are a cause of congenital hypothyroidism non-goitrous type 2 (CHNG2). PAX8 rearrangement and fusion with PPARgamma1 are associated with the development of thyroid tumors of follicular cell derivation.

Germinal

-R31H (Sporadic, Hypoplasia, Hypothyroid)

-Q40P (Sporadic, Hypoplasia, Hypothyroid)

-C57Y (Familial, Hypoplasia, Hypothyroid)

-L62R (Familial, Hypoplasia, Cystic rudiment, Hypothyroid)

-R108TER (Sporadic, Ectopia with hypoplasia, Elevated TSH, elevated TG)

-R31C

-R52P

-S54G

-S48F

-T225M

-F329L (Polymorphism)

-c.989_992delACCC

Somatic

t(2;3)(q13;p25): PAX8/PPARgamma Fusion Gene

Implicated in

Thyroid tumors

Note

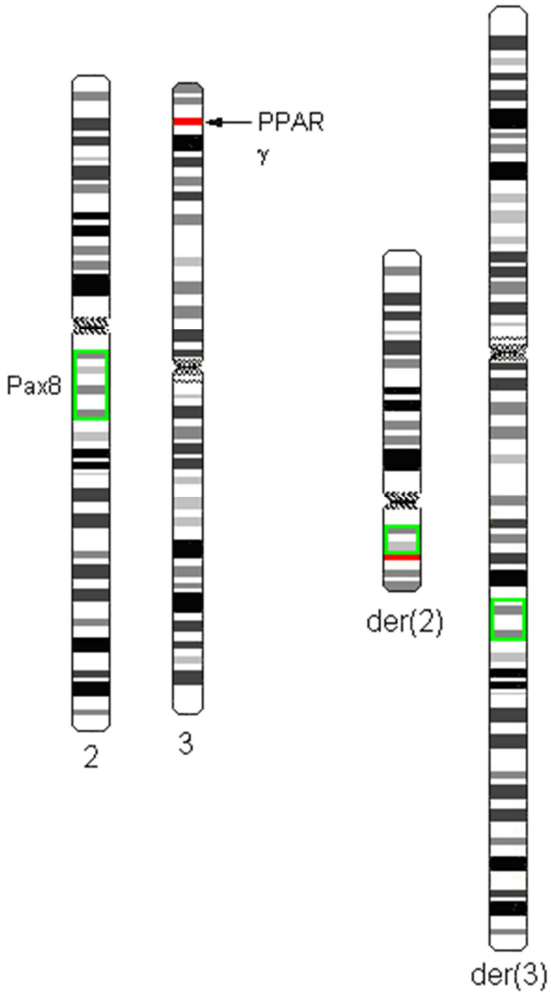
PAX8/PPARgamma1 is an oncoprotein resulting from fusion of the DNA-binding domains of PAX8 to domains A to F of the peroxisome proliferator-activated receptor gamma-1 (PPARgamma1). It involves a chromosome 3p25 and 2q13 transloca-tion, creating a fusion gene. This encompasses the promoter and the proximal coding portion of PAX8 gene and most of the coding sequence of the PPARgamma1 gene. PPARgamma1 maps to 3p25, which is a breakpoint hot spot region for thyroid tumors of follicular cell origin (follicular carcino-mas and adenomas).

Cytogenetics

t(2;3)(q13;p25). Fine mapping and molecular characterization of the 2q13 and 3p25 translocation breakpoint regions revealed fusion between exons 1 to 7, 1 to 8, or 1 to 9 of PAX8 (2q13) and exons 1 to 6 of PPARgamma1 (3p25).

Abnormal protein

PAX8/PPARgamma1 (PPFP)

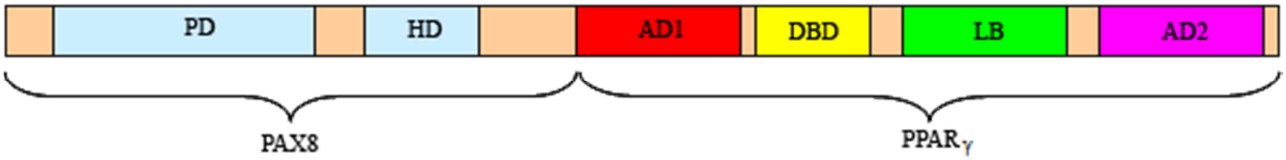


Oncogenesis

Translocations or inversions can give rise to the activation of an oncogene through its positioning near a strong promoter or its fusion with another gene, endowing the fused transcript with tumori-genic properties.

PAX8 is a transcription factor with a key role in the maintenance of a differentiated phenotype in thyroid follicular cells. PPARgamma is a ligand dependent nuclear transcription factor highly expressed in adipose tissue.

The PAX8 promoter, which is active in thyroid follicular cells, drives the expression of PAX8/ PPARgamma1 fusion protein (PPFP). Since no point mutations in the PPARgamma1 gene have been found in thyroid carcinomas and cell lines, it is speculated that PPARgamma1 activation resulting from the rearrangement plays a direct oncogenetic role. Reduced expression of normal PAX8 protein may also contribute to tumor development.



PD: Paired Homeobox (DNA Binding Domain); HD: Partial Homeobox; AD: Activation Domain; DBD: DNA Binding Domain; LB: Ligand Binding

In fact, PPFP oncogenic effects could relate to constitutive overexpression of the full length PPARgamma1 domain, interference with wild-type PPARgamma1 or PAX8 function, novel intrinsic properties of PPFP, or a combination of the above. PPARgamma1 is thought to be the principal target of a class of antidiabetic agents (thiazolidinediones) and PPFP inhibits thiazolidine-dione-induced gene transactivation by wild-type PPARgamma1. PAX8/PPARgamma1 has been identified in thyroid tumors of follicular cell deriva-tion characterized by a well developed follicular pattern of growth. These tumors are usually follicular carcinomas but may also be follicular variant papillary carcinomas or follicular adenomas. It has therefore been suggested that PAX8/ PPARgamma1 represents an early event in follicular cell tumorigenesis. Diagnosis of thyroid malignancies with a follicular growth pattern is primarily based on the identification of capsular or vascular invasion, which can only be assessed by histopathological examination of the surgically removed specimen. As a consequence, many individuals diagnosed with a follicular-patterned thyroid neoplasm undergo surgery. Since PAX8/ PPARgamma1 is associated with a diagnosis of carcinoma, identification of the rearrangement may prove a useful tool for molecular diagnosis.

Thyroid follicular carcinoma

Note

PAX8/PPARgamma1 has been identified in thyroid tumors of follicular cell derivation characterized by a well developed follicular pattern of growth. These tumors are usually follicular carcinomas but may also be follicular variant papillary carcinomas or follicular adenomas.

Disease

Thyroid follicular carcinoma is a malignant epithelial tumor showing evidence of follicular cell differentiation and lacking the diagnostic nuclear features of papillary carcinoma.

Prognosis

PAX8/PPARgamma1 is detected in ~30-40% of thyroid follicular carcinomas. Follicular carcinomas with PAX8/PPARgamma1 are angioinvasive and may be aggressive.

Papillary thyroid carcinoma, follicular variant

Note

PAX8/PPARgamma1 has been identified in some papillary thyroid carcinomas, follicular variant (up to 30% in some series).

Disease

A malignant epithelial tumor showing evidence of follicular cell differentiation and characterized by distinctive nuclear features (enlargement, oval shape, elongation and overlapping). Follicular variant papillary carcinoma is composed of folli-cular structures without well developed papillae.

Thyroid follicular adenoma

Note

PAX8/PPARgamma1 has been identified in ~5-10% of thyroid follicular adenoma.

Disease

A benign, encapsulated tumor of the thyroid showing evidence of follicular cell differentiation.

Prognosis

Thyroid follicular adenomas are benign tumors.

Wilms' tumor

Note

PAX8 is expressed in Wilms' tumor and it is potentially involved in its induction. Pax-8 gene product resides upstream of wt1 in a common regulatory pathway. Two PAX8 isoforms, genera-ted by alternative splicing at the C-terminus, were found to be capable of activating wt1 expression. PAX8 function during mesenchymal-epithelial cell transition in renal development is to induce wt1 gene expression.

Disease

Wilms' tumor, or nephroblastoma, is a malignant embryonal neoplasm of the kidney derived from nephrogenic blastemal cells that replicate the histology of the developing kidney. The tumor often shows divergent differentiation patterns. It is characterized by abortive tubules and glomeruli, surrounded by a spindled cell stroma. The stroma may include striated muscle, cartilage, bone, fat tissue. The genes predisposing to Wilms' tumor are WT1 and WT2.

Prognosis

Wilms' tumor is aggressive but potentially curable.

Ovarian carcinoma

Note

Aberrant transcriptional expression of PAX8 has been reported in epithelial ovarian cancer.

Disease

Malignant tumors of the ovary derived from the ovarian surface epithelium or its derivatives.

Acute myeloid leukaemia

Note

PAX8 (with PAX2) may be a candidate for the upregulation of WT1 in a proportion of Acute myeloid leukaemias.

Disease

Acute myeloid leukemia is a neoplasm of myeloid blasts in bone marrow, blood or other tissue.

Congenital hypothyroidism non-goitrous type 2 (CHNG2)

Note

Several PAX8 mutations have been identified

located in the conserved paired domain of PAX8.

Disease

Congenital hypothyroidism non-goitrous type 2 (CHNG2) is a congenital form of hypothyroidism due to thyroid dysgenesis (athyreotic hypothyro-idism), while congenital hypothyroidism non-goitrous type 1 (CHNG1) is due to resistance to thyroid-stimulating hormone (TSH).

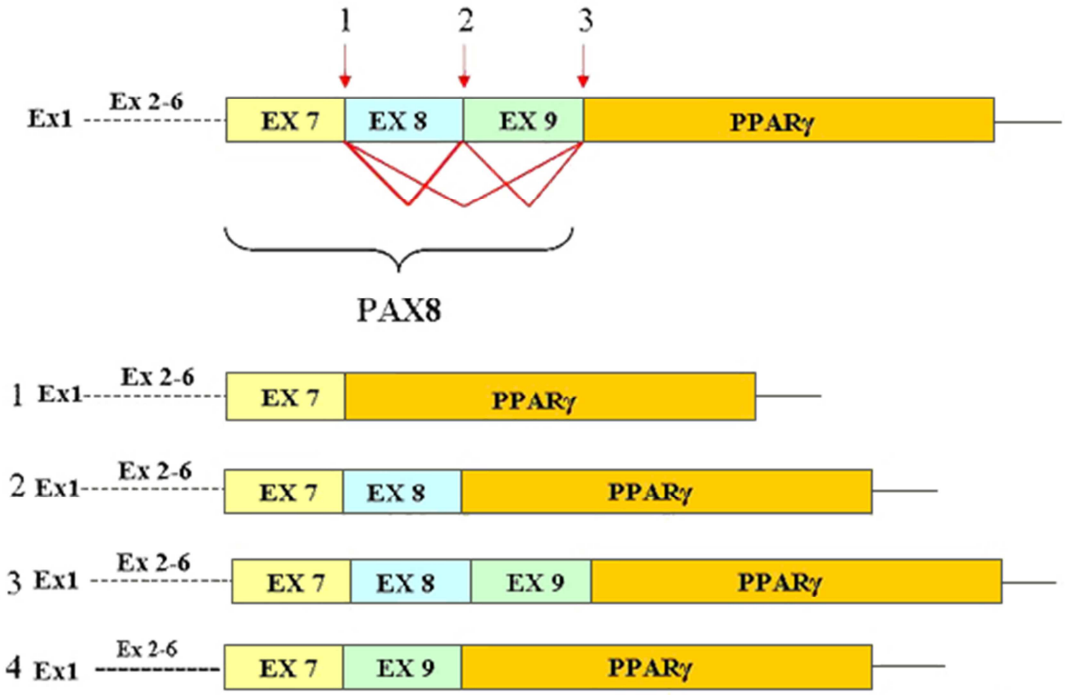
Primary congenital hypothyroidism is usually sporadic but if caused by organification defects is often recessively inherited.

The mutant proteins have markedly reduced DNA binding with subsequent loss of transcriptional activation function. The mutations are thought to disrupt the pronounced gain of alpha helical PAX8 content that follows the interaction of PAX8 with DNA: they impair the unstructured to structured transition that occurs during DNA recognition (loss of "induced fit"). As a result of the mutations PAX8 protein cannot perform its role in activating transcription of its target-genes, such as TG, TPO and NIS.

Marked phenotypic variability has been found within affected families, suggesting variable penetrance and expressivity of PAX8 gene defects.

Some PAX8 mutations cause congenital hypothyro-idism, while others mildly reduce thyroid hormone levels or have no detectable effect. Accordingly, thyroid glands of patients with PAX8 mutations are often small and hypoplastic, sometimes completely absent (athyreosis), suppor-ting the concept that PAX8 mutations disrupt the normal growth and survival of thyroid cells during embryonic development. The reduced thyroid parenchymal mass may be unable to produce the required amounts of thyroid hormone. However, normal thyroid glands have also been reported in patients carrying PAX8 mutations. A small deletion (c.989_992delACCC) in exon 7 causing a frame-shift with premature stop codon after codon 277 has been described in a patient with congenital hypothyroidism and thyroid hypoplasia.

Breakpoints



PAX8/PPARgamma1 breakpoints and chimeric mRNA.

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