

Solid Tumour Section

Mini Review

Thyroid: Papillary carcinoma

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Published in Atlas Database: August 2000

Online updated version : <http://AtlasGeneticsOncology.org/Tumors/PapilThyroidCarID5053.html>

DOI: 10.4267/2042/37675

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Classification

Note

Papillary Thyroid Carcinomas (PTCs) derives from the thyroid follicular cells, as the other type of well-differentiated thyroid carcinomas, the follicular ones; however these differentiated thyroid cancers are regarded as different entities:

The follicular carcinoma, solitary and encapsulated, is associated with endemic goiter, a diet with low iodine intake and metastatizes almost exclusively via the blood stream, often to bones.

The papillary carcinoma, on the contrary, is multifocal and associated with a previous radiation exposure, high iodine intake and metastatizes through lymphatic spread to regional lymph-nodes.

Cytogenetics

Cytogenetics Morphological

Seventy cases of papillary thyroid carcinomas (PTCs) have been reviewed, 51 of them displaying a normal karyotype (73%). In 10 cases non recurrent structural

or numerical changes were observed. In particular, 9 cases showed recurrent structural changes including: inv10(q11.2q21.2) in 5 tumors, a t(10;17)(q11.2;q23) in two cases, and a der(1) in the last two tumors.

Genes involved and proteins

Note

These abnormalities represent the cytogenetic mechanisms which activate the receptor tyrosine kinase (RTK) proto-oncogenes RET on chromosome 10 and NTRK1 on chromosome 1, respectively.

The alternative involvement of the RET and NTRK1 tyrosine kinases receptors in the development of a consistent fraction (45%) of PTCs has been demonstrated.

Somatic rearrangements, both intra and interchromosomal, of RET and NTRK1 produce several forms of oncogenes.

In all cases, RET or NTRK1 tyrosine kinase (TK) domains are fused to the amino-terminus of different gene products. The latter have been defined as 'activating' genes.

Oncogenic rearrangements of RET proto-oncogene (10q11.2) and NTRK1 proto-oncogene (1q22) in papillary thyroid carcinoma

<i>Oncogene</i>	<i>Protooncogene</i>	<i>Activating gene (Chromosome)</i>	<i>Fusion product</i>
PTC-1	RET	H4/D10S170 (10q21)	p59-p64
PTC-2	RET	R1a(PKA) (17q23q24)	p76-p81
PTC-3	RET	ELE1 (10q11.2)	p75-p80
TRK	NTRK1	TPM3 (tropomyosin) (1q31)	p70
TRK-T1/T2	NTRK1	TPR (1q25)	p55/p150
TRK-3	NTRK1	TFG (3q12)	p68

RET**Location**

10q11.2

Protein

The RET proto-oncogene codes for the tyrosine kinase receptor of GDNF (Glial cell Derived Neurotrophic Factor) and Neurturin (NTN); activation of RET by GDNF or NTN has been shown to require one of two accessory proteins, GDNFRa and GDNFRb.

Germinal mutations

Germline mutations of proto-RET result in human diseases including familial medullary thyroid carcinoma MTC, multiple endocrine neoplasia type 2A and 2B (MEN2A and MEN2B) and Hirschsprung's disease.

Somatic mutations

RET is expressed in the thyroid by normal C cells and their pathologic counterpart, medullary thyroid carcinoma (MTC); moreover, RET expression can be detected in normal adrenal medulla and pheochromocytomas.

H4/D10S170**Location**

10q21

AKAP10 (subunit RI-a of Protein Kinase A)**Location**

17q23

ELE1**Location**

10q11

NTRK1**Location**

1q22

DNA / RNA

The NTRK1 proto-oncogene encodes the high affinity receptor for Nerve Growth Factor (NGF).

Protein

NTRK1 is primarily expressed in the nervous system.

Germinal mutations

Mice carrying a germline mutation that eliminates NTRK1 show severe sensory and sympathetic neuropathies, including the loss of neurons of the dorsal root ganglia associated with nociceptive functions, and most die within one month of birth; interestingly, point mutations leading to the inactivation of the NTRK1 receptor, have been identified in patient with CIPA (Congenital Insensitivity to Pain with Anhidrosis), an autosomal-recessive disorder characterized by absence of reaction to noxious stimuli; thus NGF signalling via NTRK1

appears essential for the development and maintenance of both the peripheral and central nervous systems.

TPM3**Location**

1q22-23

TPR**Location**

1q25

TFG**Location**

3q12

Result of the chromosomal anomaly**Hybrid Gene****Note**

The RET/PTC1 oncogene, represents the first example of oncogene activation in solid tumors due to an acquired chromosomal abnormality.

Description

RET/PTC1 is a chimeric transforming sequence generated by the fusion of the TK domain of RET to the 5' terminal sequence of the gene H4/D10S170; both partners in the fusion have been localized to chromosome 10q and their fusion is the molecular event consequent to a paracentromeric inversion of chromosome 10q, inv 10 (q11.2q21.2).

Fusion Protein**Oncogenesis**

H4/D10S170 has been shown to display a coiled-coil sequence which confers to the oncoprotein the ability to form dimers, resulting in a constitutive activation of the TK function.

Hybrid Gene**Note**

A second example of RET activation is the RET/PTC2 oncogene; the cytogenetic analysis of one case of RET/PTC2 positive carcinoma revealed that this oncogene arises from a t(10;17)(q11.2;q23) reciprocal translocation.

Description

In this case the rearrangement involved the gene of the regulatory subunit RI-a of Protein Kinase A, which maps to chromosome 17q23.

Fusion Protein**Oncogenesis**

Interestingly, like the H4 gene, RI-a also contains a dimerization domain and the construction of RET/PTC2 mutants with deletions in RI-a, has demonstrated that the formation of dimers is necessary to express the activity of the oncogene.

Hybrid Gene

Note

Finally, a third example of RET activation in PTCs has been reported, RET/PTC3; also in this case, a paracentric inversion of the long arm of chromosome 10 was identified.

Fusion Protein

Oncogenesis

In this oncogene, the TK domain of RET is fused to sequences derived from a previously unknown gene named ELE1 (otherwise named RFG). ELE1 is localized in the same chromosomal region of RET, 10q11.2.

Hybrid Gene

Note

Several cases of PTCs showed an activation of the NTRK1 proto-oncogene; in three specimens a chimeric sequence generated by the rearrangement of an isoform of non-muscle tropomyosin (TPM3) and NTRK1 was identified; the former has been mapped to chromosome 1q22-23; therefore, the NTRK1 localization on 1q22 suggested that a 1q intrachromosomal rearrangement could have generated the TRK oncogene.

Description

Molecular analysis of TRK positive PTCs revealed the presence, not only of the product of the oncogenic rearrangement (5'TPM3-3'NTRK1), but also of that related to the reciprocal event (5'NTRK1-3'TPM3); this finding indicates that an intrachromosomal inversion, inv(1q), provided the mechanism of the NTRK1 oncogenic activation in these tumors.

Note

In the remaining cases genes different from TPM provided the 5' terminus of the oncogene; therefore the latter were designated as TRK-T.

Three cases showed the fusion of NTRK1-TK domain to sequences of the TPR (Translocated Promoter Region) gene, originally identified as part of the MET oncogene.

Description

The first of these cases, TRK-T1, is encoded by a hybrid mRNA containing 598 nucleotides of TPR and 1148 nucleotides of NTRK1; the TPR locus is on chromosome 1q25; therefore, as for TRK, an intrachromosomal rearrangement, molecularly defined as an inversion of 1q, is responsible for its formation; a

rearrangement involving the same two genes, TPR and NTRK1, has been found in two other papillary thyroid tumors; although the two rearrangements involve different genomic regions of the partner genes, they occur in the same intron of both TPR and NTRK1; as a consequence, the same mRNA and 1323 aminoacid oncoprotein are produced and designated TRK-T2 in both cases; similarly to TRK-T1, the molecular characterization of these rearrangements indicated the chromosomal mechanism leading to the oncogenic activation as an inv(1q).

Note

As for the last two oncogenes derived from NTRK1 activation, one is still uncharacterized whereas the other, designated TRK-T3, has recently been analyzed.

Description

Sequence analysis revealed that TRK-T3 contains 1412 nucleotides of NTRK1 preceded by 598 nucleotides belonging to a novel gene named TFG (TRK Fused Gene) encoding a 68 kDa cytoplasmic protein; the latter displays, in the TFG part, a coiled-coil region that endows the oncoprotein with the capability to form complexes, as shown by the TK domains; in this condition, the latter can recruit SH2 and SH3 containing cytoplasmic effector proteins.

To be noted

Note

In fact Ret/ptcs oncoproteins and in some cases Trk oncoproteins were demonstrated to bind and activate PLC γ , an SH2-containing enzyme catalyzing the hydrolysis of phosphatidylinositol biphosphate to inositol trophosphate and diacyl glycerol, and Shc, an adaptor protein belonging to the Ras pathway; the relocalization in the cytoplasm of RET and NTRK1 enzymatic activity could allow their interaction with unusual substrata, perhaps modifying their functional properties.

References

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This article should be referenced as such:

Pierotti MA. Thyroid: Papillary carcinoma. *Atlas Genet Cytogenet Oncol Haematol*. 2000; 4(4):209-211.
