RET (REarranged during Transfection)

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Identity
HGNC (Hugo): RET
Location: 10q11.2
Note: proto-oncogene.

DNA/RNA
Description
21 exons, 3415 pb.

Transcription
3 mains alternative spliced mRNA in the 3’ region.

Protein
Description
Several isoforms; 3 main isoforms detected in human:
Long isoform (RET51): 1114 amino acids;
Middle isoform (RET 43): 1106 amino acids;
Short isoform (RET 9): 1072 amino acids.

Expression
RET is mainly expressed in tumors of neural crest origin: medullary thyroid carcinoma, pheochromocytoma, neuroblastoma.
In human embryos, RET is expressed in a cranial population of neural crest cells, and in the developing nervous and urogenital systems.
RET expression is found in several crest-derived cell lines, spleen, thymus, lymph nodes, salivary glands, spermatogonia, and recently in normal thyroid tissue, thyroid adenoma and both papillary and follicular thyroid cell neoplasias.

Function
RET is a tyrosine kinase receptor whose ligands are neurotrophic factors of the glial-cell line derived neurotrophic factor (GDNF) family, including GDNF, neurturin, artemin and persefin. RET activation is mediated via different glycosyl phosphatidylinositol-linked GRF receptors.

Homology
General structure is similar to other tyrosine kinase receptors but RET differs by the presence of a cadherin domain in its extracellular region.

Mutations

Germinal
Germline RET mutations causes autosomal dominant inherited multiple endocrine neoplasia type 2 (MEN2) and familial medullary thyroid carcinoma only (FMTC). All these mutations are missense activating mutations. They are widely dispersed in 7/21 exons of RET with phenotype-genotype relationships: mutations in exon 11 are strongly associated with MEN2A phenotype, mutations in exon 16 or exons 8, 10, 13, 14, 15, with NEM2B and FMTC (rarely NEM2A) phenotypes respectively.
Germline RET mutations are associated to the autosomal inherited Hirschprung's disease or colonic aganglionosis (HSCR) which represents 15-20% of HSCR cases. RET mutations are loss-of-function mutations dispersed throughout the RET coding sequence and include deletions, insertions, frameshift missense and nonsense mutations.

Somatic
Somatic RET mutations have been identified in sporadic medullary thyroid carcinoma (MTC) and pheochromocytoma, mostly located in exon 16 at codon 918 (30-70% of sporadic MTC). Somatic mutations in exons 15, codon 883 and in exon 13,
codon 766 have been also detected in rare cases of sporadic MTC.

Somatic rearranged forms of RET (RET/PTC) are detected in human papillary thyroid carcinoma (PTC): several activating genes rearrange with RET to form RET/PTC by juxtaposing the genomic region coding for the tyrosine kinase domain with the 5’-terminal regions of several unrelated genes: H4: PTC1; Rla: PTC2; ELE1: PTC3/4; RFG5: PTC5; hTIF1: PTC6; RFG7: PTC7, and ELKS.

RET rearrangement as RET/PTC1 is mostly detected in typical sporadic papillary thyroid carcinoma, RET/PTC3 occurred at high frequency in childhood papillary thyroid carcinoma from areas contaminated by the Chernobyl nuclear reactor accident.

**Implicated in**

*Multiple Endocrine Neoplasia type 2 (MEN2), Hirschprung’s disease (HSCR).*

**Somatic rearranged forms of RET (RET/PTC) are detected in human papillary thyroid carcinoma.**

**Disease**

MEN 2A (60% of MEN2) associates medullary thyroid carcinoma (MTC) (100% of the cases) with pheochromocytoma in 50% of cases and with primary hyperparathyroidism (pHPT) in 5 to 20% of cases.

MEN 2B (5% of MEN2) is characterized by the association of MTC (100% of the cases) with pheochromocytoma (about 50% of the cases) as well as a phenotype including skeletal abnormalities suggestive of Marfan syndrome and the presence of multiple mucosal neuroma; no pHPT is found in MEN 2B.

Familial MTC only (FMTC) represents 35% of MEN 2 and is characterized by the absence of other associations throughout the entire follow up.

Hirschprung's disease or aganglionosis (HSCR) is a frequent congenital intestinal malformation (1/5000 live births) characterized by the absence of neural crest-derived parasympathetic neurons of the hindgut.

Typical sporadic papillary thyroid carcinoma and childhood papillary thyroid carcinoma linked to radiation exposure are associated with somatic RET/PTC rearrangements.

**Prognosis**

The prognosis of MEN2 and FMTC is related to MTC: it depends mainly on the histopathological stage of the MTC disease.

**References**


*This article should be referenced as such:*