

# Ret

## Key References

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## Overview

The human RET (REarranged during Transfection) gene maps on chromosome 10 q11.2 and codes for a single-pass transmembrane protein. Its extracellular portion contains four cadherin-like repeats, a calcium-binding site and a cysteine-rich domain. The intracellular portion features a typical tyrosine kinase domain. Two major protein products (RET-9 and RET-51) are generated through an alternative splicing mechanism. RET is the functional receptor for ligands of the glial cell-line derived neurotrophic factor (GDNF) family. Four GDNF family ligands (GFL) have been isolated: GDNF, neurturin (NRTN), artemin (ARTN) and persephin (PSPN). GFLs bind RET in conjunction with glycosylphosphatidylinositol (GPI)-anchored co-receptors designated "GDNF family receptor- $\alpha$ " (GFR- $\alpha$ ). Each of the four GFLs uses one of the four GFR- $\alpha$  (GFR- $\alpha$  1-4) as preferential receptor. GFLs form a high-affinity complex with the corresponding GFR- $\alpha$  homodimer, and the complex brings together two RET molecules thereby triggering autophosphorylation and intracellular signaling. RET contains at least 12 autophosphorylation sites. A complex network of intracellular signaling pathways follows the autophosphorylation of some of them. RET tyrosines 905, 981, 1015 and 1062 are docking sites for Grb7/10 proteins, c-Src, phospholipase C $\gamma$  and Grb2, respectively. Tyrosine 1062 recruits many proteins including Shc/N-Shc, FRS2, IRS1/2, DOK1/4/5 and enigma. Thus, RET appears to trigger a complex network of intracellular signaling pathways with Tyrosine 1062 being central to most of them.

RET is expressed primarily in peripheral enteric, sympathetic and sensory neurons, and in central motor, dopaminergic and noradrenergic neurons. It is also expressed in branching ureteric bud during embryo-

genesis and in differentiating spermatogonia. RET is essential for the development of the sympathetic, parasympathetic and enteric nervous systems (ENS) and the kidney. In humans, RET loss-of-function mutations cause about 50% of familial megacolon (Hirschprung's disease, HSCR) and 15-35% of sporadic HSCR cases. Mutations identified in the RET extracellular domain markedly impair cell surface expression of the protein, probably because of incorrect folding. Mutations in the kinase domain virtually abolish RET enzymatic activity. Finally, a few mutations in the RET carboxyl-terminal tail impair binding to adaptors, i.e., Shc, FRS2, IRS1 and ShcC (Rai/N-Shc).

Activating germline point mutations in RET cause three related dominantly-inherited cancer syndromes: multiple endocrine neoplasia type 2A (MEN 2A), 2B (MEN 2B) and familial medullary thyroid carcinoma (FMTC). MEN 2 patients are affected by medullary thyroid carcinoma (MTC), a malignant tumor arising from calcitonin-secreting C cells of the thyroid gland. Additional features can be present in MEN 2A and MEN 2B, but not FMTC patients. FMTC patients usually develop MTC at a later stage in life. Most MEN 2B patients carry the M918T mutation in the RET kinase domain. Most MEN 2A and FMTC mutations affect one cysteine in the extracellular cysteine-rich domain of RET. MEN 2A is associated most frequently with mutations of codon 634 (85%), whereas FMTC mutations are evenly distributed among the various cysteines.

MEN 2-associated RET mutations have a gain-of-function effect, i.e., they promote activation of the kinase and oncogenic conversion. Indeed, MEN 2 was the first

example of an inherited cancer syndrome caused by the germline transmission of a dominantly activated oncogene. Mechanisms leading to RET oncogenic conversion in MEN 2 depend on the location of the amino-acid change. Extracellular cysteine mutants display constitutive kinase activity consequent to disulfide-bonds stabilized homodimerization. These cysteine residues are thought to be normally involved in the formation of intramolecular disulfide bonds. Thus, when a cysteine is mutated, a partner cysteine may become free and form an aberrant intermolecular bond between two mutated RET monomers.

The first evidence of RET involvement in human cancer was obtained in thyroid gland papillary carcinomas. Chromosomal inversions or translocations of 10q11.2 occur in 2.5% to 40% of papillary thyroid carcinomas (PTC) and cause the recombination of the kinase-encoding domain of RET with heterologous genes thereby generating the RET/PTC oncogenes. RET/PTC 1 (H4-RET fusion) and 3 (RFG-RET fusion) are the most prevalent variants. RET/PTC rearrangement cause a ligand-independent activation of RET oncogenic signaling. A body of evidence supports the notion that RET/PTC oncogenes can be causative in thyroid tumorigenesis and also an early genetic change in PTC development.

RET is a suitable target for the design of novel therapeutic approaches for human cancer. Accordingly, several small-molecule ATP-mimetics, including PP1, PP2, ZD6474, CEP-701, CEP-751, RPI-1, have been demonstrated to efficiently (at concentrations in the nanomolar range) obstruct RET enzymatic function.

# Ret

<b>FAMILY MEMBERS</b>	RET
<b>OTHER NAMES</b>	CDHF12, D-ret, Dret, Hirschsprung disease: HSCR1, MEN2A, MEN2B, MTC1, multiple endocrine neoplasia and medullary thyroid carcinoma 1, PTC, RET51, RET9
<b>MOLECULAR WEIGHT/ STRUCTURAL DATA</b>	123 kDa 1114 aa (RET-51, human), 1072 aa (RET-9, human)
<b>ISOFORMS</b>	Not known
<b>SPECIES</b>	Human, mouse, <i>Xenopus</i> , rat, dog, <i>Drosophila</i> , chicken
<b>DOMAIN ORGANIZATION</b>	Cadherin domain, N-terminal extracellular domain, a cysteine-rich extracellular domain, C-terminal cytoplasmic tyrosine kinase domain
<b>PHOSPHORYLATION SITES</b>	Tyr <sup>806</sup> , Tyr <sup>809</sup> , Tyr <sup>900</sup> , Tyr <sup>905</sup> , Tyr <sup>981</sup> , Tyr <sup>1015</sup> , Tyr <sup>1062</sup> , Tyr <sup>1090</sup> , Tyr <sup>1096</sup>
<b>TISSUE DISTRIBUTION</b>	Peripheral and central nervous system, thyroid C-cells, adrenal medulla developing ureteric bud, spermatogonia
<b>SUBCELLULAR LOCALIZATION</b>	Not known
<b>BINDING PARTNERS/ ASSOCIATED PROTEINS</b>	DOK4, DOK5, PLC- $\gamma$ , DOK1, DOK3, DOK6, DOK2, FRS2, GRB2, Grb10, Shc, N-Shc, c-Src, IRS 1/2, Gab 1/2
<b>UPSTREAM ACTIVATORS</b>	GDNF, PAX3, SOX10, NRTN, ARTN, PSPN
<b>DOWNSTREAM ACTIVATION</b>	Raf/MAP kinase, PI3K/Akt, PLC $\gamma$ , c-Src, STAT3 Rac/c-Jun-terminal kinase, Shc, Braf, PDK1
<b>INHIBITORS</b>	PP1, PP2, ZD6474, CEP-701, CEP-751, RPI-1
<b>ACTIVATORS</b>	Not known
<b>SELECTIVE ACTIVATORS</b>	Not known
<b>PHYSIOLOGICAL FUNCTION</b>	Neuronal cells survival and differentiation, kidney morphogenesis, spermatogonia differentiation
<b>DISEASE RELEVANCE</b>	Hirschsprung's disease (congenital magacolon) (HSCR), multiple endocrine neoplasia type 2 syndromes (MEN2A, MEN2B, FMTC), sporadic medullary thyroid carcinomas (MTC), thyroid papillary carcinomas, congenital hypoventilation syndrome

## Abbreviations

**ARTN:** Artemin  
**NRTN:** Neurturin  
**PSPN:** Persephin

## FOOTNOTES