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Gene Section
Review

RET (REarranged during Transfection)

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Abstract

Review on RET gene and protein, a membrane tyrosine kinase receptor involved in various cancers, including papillary thyroid carcinoma, lung cancer, breast cancer, colorectal cancer, salivary glands cancer, skin melanomas/spitz tumors and soft tissue sarcomas, but also in inherited diseases, including multiple endocrine neoplasia type 2, familial medullary thyroid carcinoma, familial pheochromocytoma predisposition, Hirschsprung disease, congenital central hypoventilation syndrome and renal hypodysplasia/aplasia 1.

Keywords

Papillary thyroid carcinoma, Lung cancer, Breast cancer; Colorectal carcinoma; Multiple endocrine neoplasia type 2; Familial medullary thyroid carcinoma; Familial pheochromocytoma predisposition; Hirschsprung disease; Congenital central hypoventilation syndrome; Renal hypodysplasia/aplasia 1; MEN2A; MEN2B; FMTC; CCHS; RHDA1; Epithelial ovarian cancer; Uterine endometrioid carcinoma; Esophageal adenocarcinoma; Gastric adenocarcinoma; Pancreatic ductal adenocarcinoma; Leukemias; Bladder urothelial carcinoma; Papillary renal cell carcinoma; Astrocytoma; Glioblastoma multiforme; Neuroblastoma; Head and neck squamous cell carcinoma; Salivary glands tumors; Prostate cancer; Skin squamous cell carcinoma; skin melanoma; Spitz tumors; Soft tissue sarcomas; Pediatric cancers.

Identity

Other names: HSCR1, MEN2A, MTC1, MEN2B, Hirschsprung disease 1, PTC, CDHF12, RET51, CDHR16

HGNC (Hugo): RET

Location: 10q11.21

Local order:
centromere <-- BMS1, LINC02623, LINC01264, MIR5100, RET, CSGALNACT2, RASGEF1A, FXYD4, HNRNPF, ZNF487 --> telomere

DNA/RNA

Transcription

Transcript (hg38), including UTRs: chr10:43,077,069-43,127,504; Size: 50,436bp on strand +; coding region: chr10:43,077,259-43,126,754 Size: 49,496 bp, according to UCSC. RET has at least 6 transcripts. In the 2 splice variants coding for a protein NM8020630 (19 exons) and NM8020975 (20 exons). Exon nineteen is partly different: exon 19 Asp1014 - Phe1072: DYLDLAASTPSDSLIYDDGLSEEETPLVDCNN APLPRALPSTWIENKLYGRISHAFTRF, versus exon 19 Asp1014 - Gly1063: DYLDLAASTPSDSLIYDDGLSEEETPLVDCNN APLPRALPSTWIENKLYG and exon 20 Gly1063 - Ser1114: MSDPNWPGESPVPLTRADGTNTGFPRYPNDS VYANWMLSPSAAKLMDTFDS.

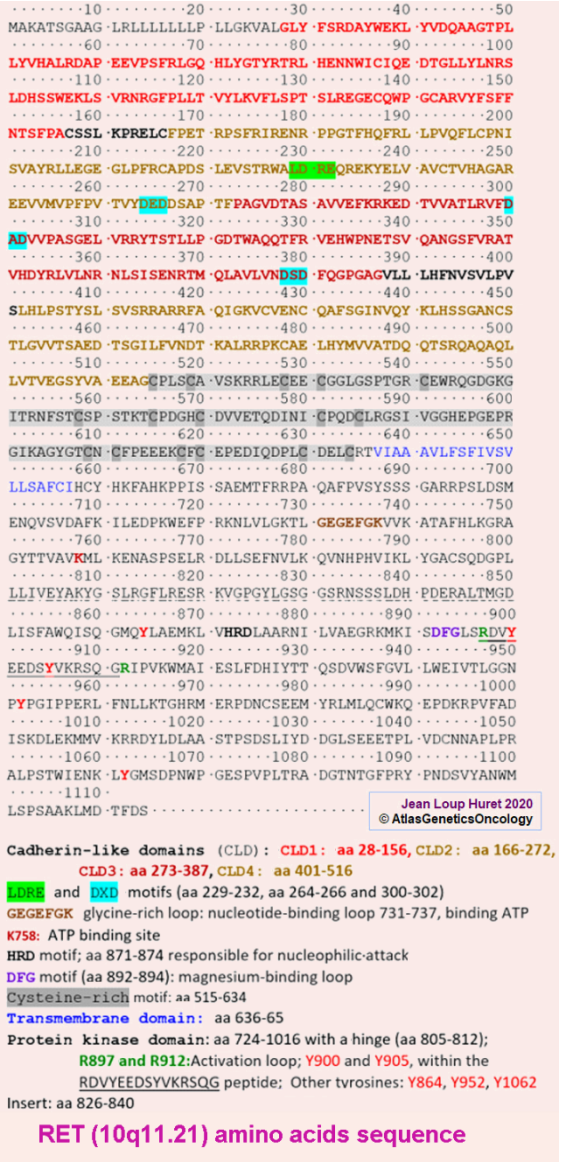

Figure 1: RET amino acids sequence with Cadherin-like, Cysteine-rich, Transmembrane and Protein kinase domains with activation loop and LDRE, DXD, GEGEFGK, HRD, and DFG motifs and tyrosines.

Protein

Description

There are three protein isoforms with 9 (RET9; short isoform, 1072 amino acids), 43 (RET43; middle isoform, 1106 amino acids), or 51 amino acids (RET51; long isoform, 1114 amino acids) from different splicing in C term.

RET is composed of an extracellular region (amino acids (aa) 29-635, coded by exons 1-10, and part of exon 11), a transmembrane region (aa 636-657, coded by part of exon 11), and a cytoplasmic region (aa 658-1114 or 1072, coded by part of exon 11, and exon 12-19 or 12-20) (Figures 1 and 2).

RET has a Signal peptide (aa 1-28). RET contains a region of RET previously reported as having similarity to cadherins and named "cadherin domain" in databases (aa 168-272, coded by part of exon 3 and part of exon 4) and a bipartite protein kinase domain separated by a hinge (aa 805-812); (aa 724-1016, coded by part of exon 12, exons 13-18, and part of exon 19).

However, a detailed study shows that there are four **cadherin-like domains** (CLD): CLD1: aa 28-156 (exon 2 and part of exon 3), CLD2 aa 166-272 (part exon 3 and part of exon 4), CLD3 aa 273-387 (part exon 4, exon 5 and part of exon 6), CLD4: aa 401-516 (part exon 6, exon 7 and beginning of exon 8), with spacer sequences between CLD1 and CLD2 and between CLD3 and CLD4 (Anders et al., 2001).

There is a **cysteine-rich domain** (CRD, aa 515-634, coded by exons 8, 9, 10 and beginning of exon-11), and a **calcium-binding sites** (CA domain, aa 229-380, coded by part of exon 4, exon 5 and part of exon 6). The cysteine- rich domain is important for receptor dimerization. The cadherin domain adopts a β -sandwich fold, and calcium-binding sites are formed in between adjacent cadherin domains by the LDRE motif (aa 229-232) of CLD2 and the DXD motifs of CLD3 (aa 264-266 and 300-302). Ca^{2+} binding is required for the interaction of RET with GDNF.

Tyrosines: **Tyrosine kinases** usually have one or two tyrosines in the activation loop, in the case of RET there are two, Y900 and Y905, within the RDVYEEDSYVKRSQG peptide, both of which can be phosphorylated. Activation loop: Y905 is required for the transforming activity and signaling of RET-MEN2A mutations.

The transforming activity of RET-MEN2B implicates Y864 or Y952. Y1062 is a multidocking site that interacts with a number of transduction molecules including SHC1, GRB2, FRS2, DOK4 / DOK5, IRS1 / IRS2, and PDLIM7. (Anders et al., 2001; Kouvaraki et al., 2005).

Other sites:

- GEGEFGK glycine-rich loop: nucleotide-binding loop 731-737, binding ATP
- K758: ATP binding site.
- DFG 892-894 motif: magnesium-binding loop
- R897 and R912: activation loop.
- HRD motif (aa 871-874) is responsible for nucleophilic attack (kinases lacking the HRD arginine are not phosphorylated in the activation loop).

Activation loop phosphorylation can counteract the positive charge of the arginine in the catalytic loop by the HRD motif.

- Leucine rich: aa 11-22.

Other remarkable sites according to Prosite:

- Protein kinase C phosphorylation sites: aa 65 (phosphoserine), 75 (phosphothreonine), 110 (S), 131 (S), 159 (S), 173 (S), 224 (S), 295 (T), 328 (T), 413 (S), 492 (T), 522 (S), 538 (T), 561 (S), 675 (T), 811 (S), 819 (S)

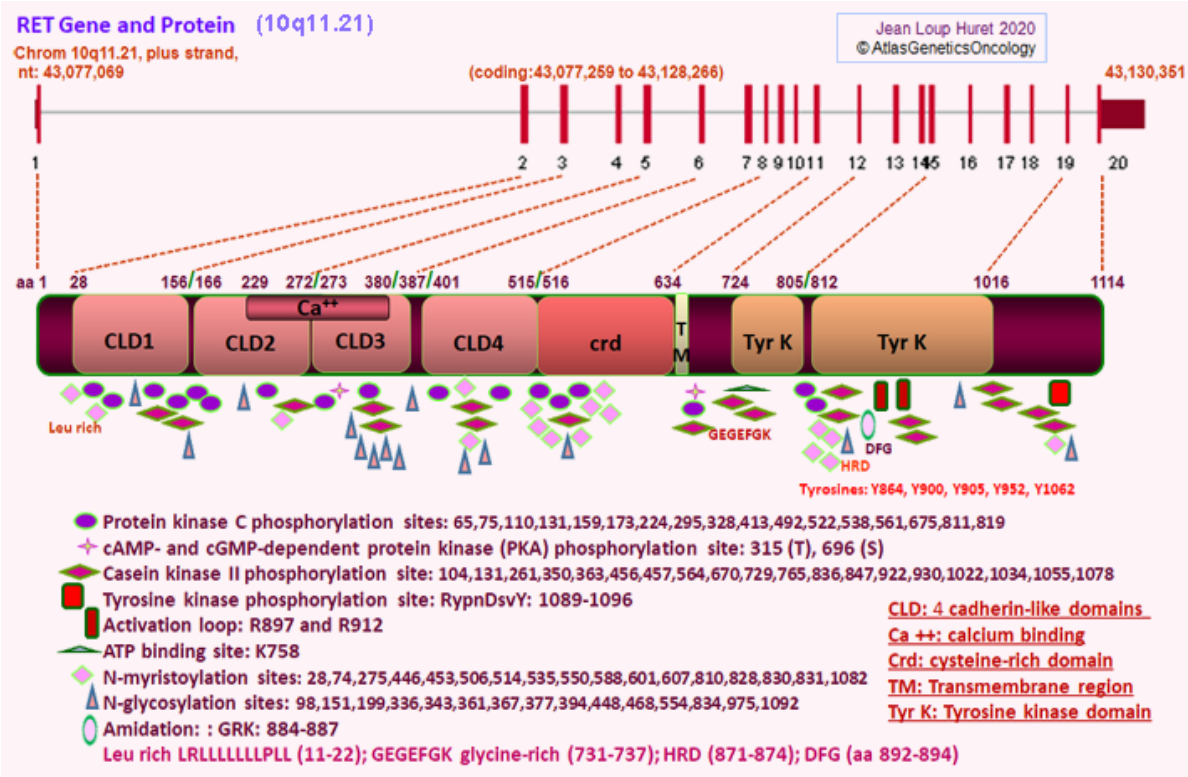

Figure 2: RET gene and protein

- cAMP- and cGMP-dependent protein kinase phosphorylation sites: 315 (T), 696 (S)
- Casein kinase II phosphorylation sites: 104 (S), 131 (S), 261 (T), 350 (T), 363 (S), 456 (T), 457 (T), 564 (T), 670 (S), 729 (T), 765 (S), 836 (S), 847 (T), 922 (S), 930 (T), 1022 (T), 1034 (S), 1055 (T), 1078 (T)
- Tyrosine kinase phosphorylation site 2: 1089-1096: RypnDsvY
- N-myristoylation sites (role in membrane targeting): 28, 74, 275, 446, 453, 506, 514, 535, 550, 588, 601, 607, 810, 828, 830, 831, 1082
- N-glycosylation sites: 98, 151, 199, 336, 343, 361, 367, 377, 394, 448, 468, 554, 834, 975, 1092

- Amidation site XGRK (protects from proteolysis): 884-887.

Expression

RET is particularly expressed in neural tissues (brain and autonomic nervous system: enteric, sympathetic, and parasympathetic), neuroendocrine cells, including thyroid C cells, adrenal medullary cells, parathyroid cells and in the developing kidney, but also in lung, digestive tract, adult kidney, female organs, male organs, skin, and blood apparatus.

Localisation

RET is localized predominantly in the plasma membrane and in the cytoplasm; RET is also localized in the nucleus, indicating that intact RET can translocate into the nucleus (Bagheri-Yarmand et al. 2015). RET staining shows strong signals in both the cytoplasm, Golgi apparatus and cell membrane, whereas Hirschsprung mutant RET shows less pronounced staining on the cell membrane and more closer to the nucleolus/endoplasmic reticulum (The Human Protein Atlas).

Function

Ligands: there are four possible ligands for RET: GDNF (glial cell line-derived neurotrophic factor), NRTN (neurturin), PSPN (persephin), and ARTN (artemin). A multimetric complex composed of RET, one of the four ligands above mentioned, and one of four different high affinity glycosyl-phosphatidylinositol-anchored co-receptors, named GDNF family receptor-alpha GFRA 1 to 4.

Co-receptors: the four RET ligands GDNF, NRTN, PSPN, and ARTN interact preferentially with GFRA1, GFRA2, GFRA3, and GFRA4, respectively. The ligand (e.g. NRTN) forms a homodimer with a cystine knot at its center and requires its co-receptor (e.g. GFRA2) to activate RET. The NRTN-GFRA2 complex is composed of a dimer of dimers with the NRTN homodimer at the center and two GFRA2 monomers attached (see figure 4). GFRAs are located in lipid rafts of the plasma membrane, and RET is recruited. GFRAs can come from the same cell as RET, or from a different cell. When the co-receptor is produced by the same cell as RET, it is termed cis signaling.

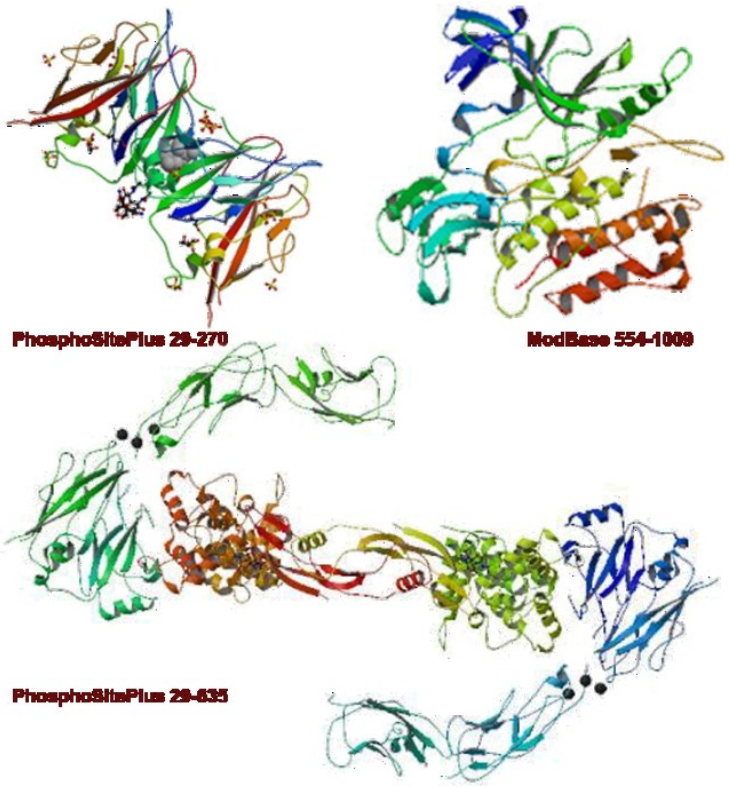

Figure 3: RET Electron Microscopy Structure 29-270 correspond to the cadherin-like domains CLD1 and CLD2 (see figure 2), 554-1009 correspond to part of crd (cysteine-rich domain), TM (transmembrane domain), and most of the tyrosine kinase domains; 29-635 correspond to the extracellular domains of RET. Images are taken from PhosphoSitePlus and ModBase: https://www.phosphosite.org//proteinAction?id=654showAllSites=true and https://modbase.compbio.ucsf.edu/modbase-cgi/model_details.cgi?searchmode=defaultdisplaymode=moddetailseq_id=model_id=a6b011e59e4a801a7295e43b8a6bc701queryfile=1589446904_9939

When the co-receptor is produced by another cell, it is termed trans signaling. Cis and trans activation of RET can occur (Reactome).

RET binding: the NRTN-GFRA2 complex binds two copies of the RET extra cellular domain ("RET-ecd") (--> RET dimerization), thereby forming a heterohexamer. RET-ecd consists of four cadherin-like domains (RET-CLD1-4) and a cysteine-rich domain (RET-crd). RET-CLD2 and RET-CLD3 coordinate calcium ions that are critical for RET folding.

Signaling: RET dimerization results in tyrosine autophosphorylation on specific tyrosine residues. (e.g. GDNF-GFRA1-activated RET is autophosphorylated at tyrosine-sites, Y981, Y1015, Y1062, and Y1096 (Note: Y1096 in found only in RET51 isoform)).

RET activates various signaling pathways, mainly through Y1062, such as PI3K/AKT/MTOR, RAS/RAF/MAPK, and JUN pathways to activate transcription factors, including EIF4EBP1, RPS6KB1, MYC, JUN, ATF1, ATF2, TP53) (Kouvaraki et al., 2005; Goodman et al., 2014; Bigalke et al., 2019).

The frequently mutated C634 in patients with MEN2A is part of the RET-crd, in which wild-type RET forms a disulfide bond with C630. The C634R mutation causes ligand-independent dimerization of RET (Goodman et al., 2014; Bigalke et al., 2019).

Phosphatases: Protein tyrosine phosphorylation is regulated by opposite activities of protein tyrosine kinases (PTKs) and phosphatases (PTPs). GDNF and GRB2 form a complex with the protein tyrosine phosphatase PTPRA. PTPRA dephosphorylates RET and inhibits the RET-RAS/RAF/MAPK signaling pathway. PTPRA also regulates the RET mutant found in MEN2A, whereas the MEN2B mutant is insensitive to PTPRA (Yadav et al., 2020). Other phosphatases are also known to balance the phosphorylation and oncogenic activity of RET: PTPRF, PTPN6 and PTPN11.

Feedback loop: ATF4 overexpression induces cell death. ATF4 promotes RET degradation and inhibits RET signaling pathways. In a feedback loop, RET represses expression of the ATF4 target proapoptotic genes PMAIP1 (known as NOXA) and BBC3 (PUMA) through phosphorylation-dependent degradation of ATF4 (Bagheri-Yarmand et al. 2015; Bagheri-Yarmand et al. 2017).

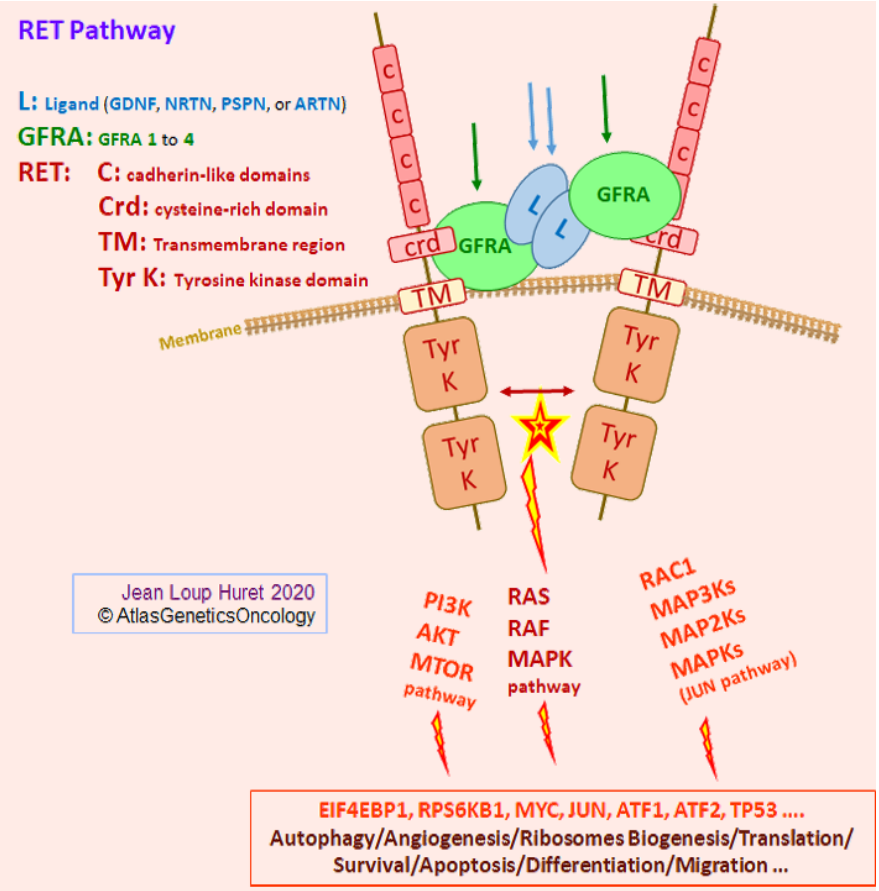

Figure 4: RET Pathway. An homodimer of Ligand (either GDNF, NRTN, PSPN, or ARTN) binds an homodimer of co-factors GFRA 1 to 4). The complex binds two RET proteins, forming a heterohexamer. RET dimerization results in tyrosine autophosphorylation which induces signaling pathways, such as PI3K/AKT/MTOR, RAS/RAF/MAPK, and JUN pathways (Figure 4). Note the so-called JUN pathway is the following RAC1 --> MAP3K proteins (misnamed MAPKKK... or JNKKK,e.g "MEKK1" or "MEKK4" for MAP3K1 and MAP3K4) --> MAP2K proteins (also called MAPKK... or JNKK, e.g "MKK4" or "MKK7" for MAP2K4 and MAP2K7) --> MAPK proteins (MAPK... or JNK, e.g "p38" or "JNK" for MAPK14 and MAPK8). Various processes are stimulated or repressed such as autophagy, angiogenesis, ribosomes biogenesis, translation, survival, apoptosis, differentiation, migration …

Mutations

Gain of function mutations affecting the extracellular cysteine-rich domain of RET result in covalent dimerization and constitutively activation of the receptor. Loss of function mutations inactivate the signaling pathway. Note: if needed, see "Nomenclature for the description of mutations and other sequence variations": http://atlasgeneticsoncology.org/Educ/NomMutID30067ES.html

RET role in the tumor microenvironment: The tumor microenvironment (TME) consists of extracellular matrix, mesenchymal cells (i.e., fibroblasts, pericytes, adipocytes and other stromal cells), immune-inflammatory cells, blood and lymphatic vessels particularly in the perineural environment.

Activation of the RET pathway has been found to be responsible for high expression and activation of cancer-associated fibroblasts-related proinflammatory proteins including cytokines, chemokines and their receptors (e.g. CCL2, CXCR4, CXCL8 (also called IL8), CXCL12, CCL20, CSF1, CSF2RA (GM-CSF), CSF3 (G-CSF), IL1B, SPP1). Cancer-associated fibroblasts promote tumorigenesis and metastasis, tumor angiogenesis and recruitment of immune-inflammatory cells (reviews in Castellone and Melillo 2018; Mulligan 2019).

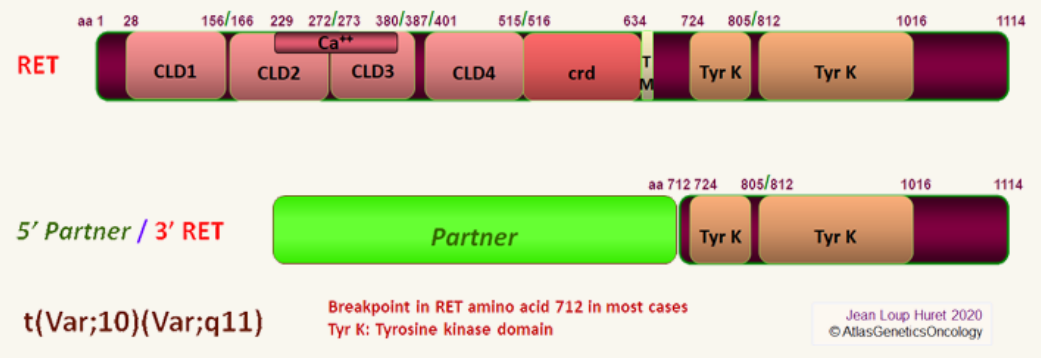

Figure 5: RET Translocations t(Var;10)(Var;q11) 5' Partner / 3' RET

Germinal

Mutations in RET have been found in various closely related inherited diseases, namely: multiple endocrine neoplasia type 2A (MEN2A), multiple endocrine neoplasia type 2B (MEN2B), familial medullary thyroid carcinomas (FMTC), familial pheochromocytoma predisposition, Hirschsprung disease, congenital central hypoventilation syndrome, and renal hypodysplasia/aplasia 1 (see below).

MEN2A/ MEN2B/ FMTC: 199 variants are described in MEN2 database (https://arup.utah.edu/database/MEN2/MEN2_display.php), of which 82 are said pathogenic. Mutations are dispersed through exons 7 to 16, many of them occurring in exons 10 or 11, in the cysteine rich domain: C609, C611, C618, C620 (exon 10), C630, D631, C634, T636, K666, D707 (exon 11). Other mutations are E505 (exon 7), C515, C531, G533, G548 (exon 8), E768, L790, Q781 (exon 13), V804 (exon 14), A883, S891, S904 (exon 15), M918, R912 (exon 16). The more common disease phenotype-specific mutations found in MEN2 are: E768D, L790F, Y791F, S891A, V804M/L (FMTC) and A883F, M918T (MEN2B). M918T catalytic domain mutants enhances autophosphorylation kinetics. M918T is a well characterized MEN2 mutation, and it correlates with the most aggressive and consistent disease phenotype (i.e. MEN2B) (Plaza-Menacho, 2017).

Somatic

Kato et al., 2017 studied 4,871 diverse cancer cases. RET aberrations were identified in 88 cases (1.8%). It was an amplification in 25% of cases (rounded numbers), a mutation in 40%, a translocation/fusion gene in 30%. Although subgroups are very small, it can be noted that mutations were found in medullary thyroid carcinoma (80%, 4 of 5 cases), paraganglioma (25%, 1/4), anaplastic thyroid carcinoma (17%, 2/12), and urothelial carcinoma (17%, 1/6). translocations/fusion genes were found in lung carcinosarcoma (17%, 1/6), papillary thyroid carcinoma (9%, 2/23) and lung adenocarcinoma (4%, 16/412), and amplifications were found in fallopian tube adenocarcinoma (8%, 1/12), uterine carcinosarcoma (5%, 1/19), and duodenal adenocarcinoma (5%, 1/20).

According to the review by Subbiah and Cote, 2020, the frequencies of somatic RET translocations/fusion genes and mutations associated with oncogenesis are the following: medullary thyroid cancer: 60-90%, papillary thyroid cancer: 10-20%, urothelial carcinoma: 16.7%, basal cell carcinoma: 12.5%, meningioma: 5.6%, non-small cell lung carcinoma: 1-2%, ovarian epithelial carcinoma: 1.9%, esophageal carcinoma: 1.4%, colorectal carcinoma: 0.7%, gastric adenocarcinoma: 0.7% , melanoma: 0.7%, and breast carcinoma: 0.2%,

in a series of 32,989 advanced cancers RET alterations included 143 in-frame fusions found in 141 patients and 33 single-nucleotide variants (SNV) resulting in an amino acid substitution found in 29 patients. RET fusions were most prevalent among patients with non-small cell lung carcinoma (NSCLC), thyroid cancer, or colorectal cancer. Seven different fusion partners (KIF5B, CCDC6, NCOA4, TRIM24, TRIM33, ERC1, APAF1) were observed. The most common fusion partner was KIF5B, which was only observed in NSCLC (n = 75) (Rich et al., 2019).

Copy number variations according to Genomic Data Commons Data Portal are: **CNV gains** in: sarcomas (11% of cases, rounded numbers), ovarian serous cystadenocarcinoma (10%), lung squamous cell carcinoma (8%), bladder urothelial carcinoma (7%), breast carcinoma (6%), lung adenocarcinoma (6%), esophageal carcinoma (6%), cholangiocarcinoma (6%), uterine carcinosarcoma (5%), adrenocortical carcinoma (4%), head and neck squamous cell carcinoma (4%), gastric adenocarcinoma (3%), hepatocellular carcinoma (3%), glioblastoma multiforme (3%), uterine endometrial carcinoma (2%), cervical carcinoma (2%), skin cutaneous melanoma (2%), colorectal adenocarcinoma (1-2%), pancreatic adenocarcinoma (1 %); **CNV losses** in: ovarian serous cystadenocarcinoma (9%), sarcomas (6%), uterine carcinosarcoma (5 %), bladder urothelial

carcinoma (5%), mesothelioma (4%), esophageal carcinoma (3%), prostate adenocarcinoma (3%), breast carcinoma (3%), adrenocortical carcinoma (2%), uterine endometrial carcinoma (2%), head and neck squamous cell carcinoma (2%),cervical carcinoma (2%), gastric adenocarcinoma (2%), lung adenocarcinoma (1%), colon adenocarcinoma (1%), hepatocellular carcinoma (1%), lung squamous cell carcinoma (1%).

Kohno et al, 2020 reviewed the mutations and fusion genes involving RET in various cancers detected in two large studies (Project Genie and TCGA PanCancer Atlas Studies):

Mutations: medullary thyroid carcinoma: 55% of cases presented a mutation in RET; breast carcinoma: 8%; of cases parathyroid carcinoma: 6 %; pheochromocytoma: 3.4 - 4.0%; T-cell lymphoblastic leukemia: 3%; lung carcinoma (neuroendocrine): 3%; upper tract urothelial carcinoma: 0,4%; uterine endometrioid carcinoma (serous/papillary serous): 0,3%.

Translocations/fusion genes: RET translocations/fusion genes result in hybrid genes and proteins (Figure 5) with constitutive dimerization and activation of RET pathways. RET translocations/fusion genes were found in: papillary thyroid carcinoma, where 1.4 - 4.4% of cases presented a gene fusion implicating RET; poorly differentiated thyroid carcinoma: 3% of cases; pleomorphic lung carcinoma: 2.5%; thyroid carcinoma (hurthle cell): 2%; anaplastic thyroid carcinoma: 1%; lung adenocarcinoma: 0.2 - 0.6%; poorly differentiated non-small cell lung carcinoma: 0.5%; colon adenocarcinoma 0.26%; gastric adenocarcinoma 0.2%; serous ovarian carcinoma: 0,17%; non-small cell lung carcinoma: 0,16%.

RET Partner Gene	Chrom.	Location: band (bp)	Translocation / fusion gene	Disease
TRIM33	**1**	1p13.2 (114392777)	t(1;10)(p13;q11) TRIM33/RET	Lung: non-small cell lung carcinoma
				Thyroid: papillary thyroid carcinoma
RASAL2		1q25.2 (178093729)	t(1;10)(q25;q11) RASAL2/RET	Soft tissue sarcoma
EML4	**2**	2p21 (42169338))	t(2;10)(p21;q11) EML4/RET	Lung: non-small cell lung carcinoma
EML6		2p16.1 (54725012	t(2;10)(p16;q11) EML6/RET	Lung: non-small cell lung carcinoma
TFG	**3**	3q12.2 (100709331)	t(3;10)(q12;q11) TFG/RET	Soft tissues: spindle cell tumors
TBL1XR1		3q26.32 (177019355)	t(3;10)(q26;q11) TBL1XR1/RET	Thyroid: papillary thyroid carcinoma
EPHA5	**4**	4q13.1 (65319563)	t(4;10)(q13;q11) APHA5/RET	Lung: non-small cell lung carcinoma
SQSTM1	**5**	5q35.3 (179820842)	t(5;10)(q35;q11) SQSTM1/RET	Thyroid: papillary thyroid carcinoma
KIF13A	**6**	6p22.3 (17763693)	t(6;10)(p22;q11) KIF13A/RET	Lung: adenocarcinoma
TRIM27		6p22.1 (28903002)	t(6;10)(p22;q11) TRIM27/RET	Salivary glands: intraductal carcinoma
				Thyroid: papillary thyroid carcinoma
				Neuro-endocrine tumor: multiple endocrine neoplasia
TBC1D32		6q22.31 (121079494)	t(6;10)(q22;q11) TBC1D32/RET	Lung: adenocarcinoma
PTPRK		6q22.33 (127968779)	t(6;10)(q22;q11) PTPRK/RET	Lung: non-small cell lung carcinoma
FGFR1OP		6q27 (166,999,317)	t(6;10)(q27;q11) FGFR1OP/RET	Chronic myeloproliferative neoplasm
CLIP2	**7**	7q11.23 (74289475)	t(7;10)(q11;q11) CLIP2/RET	Soft tissues: spindle mesenchymal neoplasm
CUX1		7q22.1 (101817602)	t(7;10)(q22,q11) CUX1/RET	Lung: non-small cell lung carcinoma
TRIM24		7q33 (138460334)	t(7;10)(q33;q11) TRIM24/RET	Lung: non-small cell lung carcinoma
				Thyroid: papillary thyroid carcinoma
TAS2R38		7q34 (141972631)	t(7;10)(q34;q11) TAS2R38/RET	Thyroid: papillary thyroid carcinoma
PCM1	**8**	8p22 (17922857)	t(8;10)(p22;q11) PCM1/RET	Lung: non-small cell lung carcinoma
				Thyroid: papillary thyroid carcinoma
RBPMS		8p12 (30384501)	t(8;10)(p12;q11) RBPMS/RET	Lung: non-small cell lung carcinoma
HOOK3		8p11.21 (42896890)	t(8;10)(p11;q11) HOOK3/RET	Thyroid: papillary thyroid carcinoma
FKBP15	**9**	9q32 (113165520)	t(9;10)(q32;q11) FKBP15/RET	Thyroid: papillary thyroid carcinoma
PRKCQ	**10**	10p15.1 (6427143)	t(10;10)(p15;q11) PRKCQ/RET	Lung: non-small cell lung carcinoma
TAF3		10p14 (7818504)	t(10;10)(p14;q11) TAF3/RET	Thyroid: papillary thyroid carcinoma

CCDC3		10p13 (12896625)	t(10;10)(p13;q11) CCDC3/RET	Lung: non-small cell lung carcinoma
PRPF18		10p13 (13586939)	t(10;10)(p13;q11) PRPF18/RET	Lung: non-small cell lung carcinoma
FRMD4A		10p13 (13643706)	t(10;10)(p13;q11) FRMD4A/RET	Lung: non-small cell lung carcinoma
KIAA1217		10p12.2 (24208791)	t(10;10)(p12;q11) KIAA1217/RET	Lung: adenocarcinoma
				Soft tissues: spindle mesenchymal neoplasm
ANKRD26		10p12.1 (27004116)	t(10;10)(p12,q11) ANKRD26/RET	Thyroid: papillary thyroid carcinoma
ACBD5		10p12.1 (27195214)	t(10;10)(p12;q11) ACBD5/RET	Thyroid: papillary thyroid carcinoma
WAC		10p12.1 (28533492)	t(10;10)(p12;q11) WAC/RET	Lung: non-small cell lung carcinoma
ARHGAP12		10p11.22 (31805398)	t(10;10)(p11;q11) ARHGAP12/RET	Lung: non-small cell lung carcinoma
KIF5B		10p11.22 (32009010)	t(10;10)(p11;q11) KIF5B/RET	Lung: non-small cell lung carcinoma
				Skin: melanomas/Spitz tumors
				Thyroid: papillary thyroid carcinoma
PARD3		10p11.22 (34109560)	t(10;10)(p11;q11) PARD3/RET	Lung: non-small cell lung carcinoma
CCNYL2		10q11.21 (42408174)	CCNYL2/RET (10q11)	Lung: non-small cell lung carcinoma
RASGEF1A		10q11.21 (43194533)	RASGEF1A/RET (10q11)	Breast cancer
RASSF4		10q11.21 (44959771)	RASSF4/RET (10q11)	Lung: non-small cell lung carcinoma
NCOA4		10q11.23 (46005088)	NCOA4/RET (10q11)	Breast cancer
				Colorectal cancer
				Lung: adenocarcinoma
				Ovary: Germ cell tumours
				Salivary glands: intraductal carcinoma
				Soft tissues: spindle cell tumors
				Thyroid: papillary thyroid carcinoma
PRKG1		10q11.23 (51074474)	PRKG1/RET (10q11)	Lung: non-small cell lung carcinoma
ANK3		10q21.2 (60026298)	t(10;10)(q11;q21) ANK3/RET	Thyroid: papillary thyroid carcinoma
SLC16A9		10q21.2 (59650764)	t(10;10))(q11;q21) SLC16A9/RET	Thyroid: papillary thyroid carcinoma
CCDC6		10q21.2 (59788748)	t(10;10)(q11;q21) CCDC6/RET	Colorectal cancer
				Lung: non-small cell lung carcinoma
				Thyroid: papillary thyroid carcinoma
CTNNA3		10q21.3 (65912518)	t(10;10)(q11;q21) CTNNA3/RET	Lung: non-small cell lung carcinoma
SIRT1		10q21.3 (67884669)	t(10;10)(q11;q21) SIRT1/RET	Lung: non-small cell lung carcinoma
RUFY2		10q21.3 (68343518)	t(10;10)(q11;q21) RUFY2/RET	Lung: non-small cell lung carcinoma
				Thyroid: papillary thyroid carcinoma
DYDC1		10q23.1 (80336106)	t(10;10)(q11;q23) DYDC1/RET	Lung: non-small cell lung carcinoma
SORBS1		10q24 (110005804)	t(10;10)(q11;q24) SORBS1/RET	Lung: non-small cell lung carcinoma
ADD3		10q25.1 (114161608)	t(10;10)(q11;q25) ADD3/RET	Lung: non-small cell lung carcinoma
CCDC186		10q25.3 (114294824)	t(10;10)(q11;q25) CCDC186/RET	Lung: non-small cell lung carcinoma
AFAP1L2		10q25.3 (126905409)	t(10;10)(q11;q25) AFAP1L2/RET	Thyroid: papillary thyroid carcinoma
DOCK1		10q26.2 (126905409)	t(10;10)(q11;q26) DOCK1/RET	Lung: non-small cell lung carcinoma
CLRN3		10q26.2 (127877841)	t(10;10)(q11;q26) CLRN3/RET	Thyroid: papillary thyroid carcinoma
PPFIBP2	**11**	11p15.4 (7513765)	t(10;11)(q11;p15) PPFIBP2/RET	Thyroid: papillary thyroid carcinoma
PICALM		11q14.2 (85957171)	t(10;11)(q11;q14) PICALM/RET	Lung: non-small cell lung carcinoma
ETV6	**12**	12p13.2 (11649854)	t(10;12)(q11;p13) ETV6/RET	Salivary glands: mammary analog secretory carcinoma
ERC1		12q13.33 (991208)	t(10;12)(q11;q13) ERC1/RET	Breast cancer
				Lung: non-small cell lung carcinoma
				Thyroid: papillary thyroid carcinoma
ANKS1B		12q23.1 (98743974)	t(10;12)(q11;q23) ANKS1B/RET	Lung: non-small cell lung carcinoma
CLIP1		12q24.31 (122271434)	t(10;12)(q11;q24) CLIP1/RET	Lung: non-small cell lung carcinoma

TSSK4	**14**	14q12 (24205720)	t(10;14)(q11;q12) TSSK4/RET	Lung: non-small cell lung carcinoma
KTN1		14q22.3 (55580207)	t(10;14)(q11;q22) KTN1/RET	Thyroid: papillary thyroid carcinoma
CCDC88C		14q32.11 (91271323)	t(10;14)(q11;q32) CCDC88C/RET	Lung: non-small cell lung carcinoma
GOLGA5		14q32.12 (92794231)	t(10;14)(q11;q32) GOLGA5/RET	Skin: melanomas/Spitz tumors
				Thyroid: papillary thyroid carcinoma
MYO5C	**15**	15q21.2 (52192318)	t(10;15)(q11;q21) MYO5C/RET	Lung: non-small cell lung carcinoma
AKAP13		15q25.3 (85380616)	t(10;15)(q11;q25) AKAP13/RET	Thyroid: papillary thyroid carcinoma
MYH10	**17**	17p13.1 (8474205)	t(10;17)(q11;p13) MYH10/RET	Soft tissues: Infantile myofibromatosis
				Soft tissues: spindle mesenchymal neoplasm
MYH13		17p13.1 (10300866)	t(10;17)(q11;p13) MYH13/RET	Thyroid: papillary thyroid carcinoma
MPRIP		17p11.2 (17042760)	t(10;17)(q11;p11) MPRIP/RET	Lung: non-small cell lung carcinoma
PRKAR1A		17q24.2 (68512379)	t(10;17)(q11;q24) PRKAR1A/RET	Lung: non-small cell lung carcinoma
				Neuro-endocrine tumor
RELCH (KIAA1468)	**18**	18q21.33 (62187291)	t(10;18)(q11;q21) KIAA1468/RET	Lung: adenocarcinoma
				Lung: non-small cell lung carcinoma
				Thyroid: papillary thyroid carcinoma
LSM14A	**19**	19q13.11 (34172447)	t(10;19)(q11;q13) LSM14A/RET	Lung: adenocarcinoma
RRBP1	**20**	20p12.1 (17613678)	t(10;20)(q11;p12) RRBP1/RET	Colorectal cancer
BCR	**22**	22q11.23 (23180365)	t(10;22)(q11;q11) BCR/RET	Chronic myeloproliferative neoplasm
SPECC1L		22q11.23 (24270817)	t(10;22)(q11;q11) SPECC1L/RET	Thyroid: papillary thyroid carcinoma
TIMP3		22q12.3 (32800816)	t(10;22)(q11 ;q12) TIMP3/RET	Soft tissues: Inflammatory myofibroblastic tumor

TABLE 1: RET and 73 translocations/fusion partners

Implicated in

Multiple endocrine neoplasia type 2A (MEN2A)

RET mutations in MEN2A are gain-of-function mutations.

Disease

Multiple endocrine neoplasia type 2A is an autosomal dominant syndrome of multiple endocrine neoplasms, including medullary thyroid carcinoma (MTC), a tumor of the calcitonin-secreting parafollicular C-cells in 100% of the cases, pheochromocytoma, a tumor of the adrenal chromaffin cells in 50% of the cases, and primary hyperparathyroidism in 20-30% of the cases. It is caused by missense mutations in RET. There is a cluster of mutations concerning six cysteines (aa 609, 611, 618, 620, exon 10 and aa 630, 634, exon 11, cysteine-rich domain) in MEN2A (Giraud, 2001; Somnay et al., 2012; Krampitz and Norton, 2014; Plaza-Menacho, 2017).

Multiple endocrine neoplasia type 2B (MEN2B)

RET mutations in MEN2B are gain-of-function mutations.

Disease

Multiple endocrine neoplasia type 2B, is an autosomal dominant syndrome defined by the presence of medullary thyroid carcinoma, pheochromocytomas, ganglioneuromatosis of the gastrointestinal tract, mucosal neuromas of the lips and tongue, and a Marfanoid habitus, but no hyperparathyroidism. It is caused by missense mutations in RET. The major mutation is M918T (coded by exon 16, tyrosine kinase domain) (Giraud, 2001; Somnay et al., 2012; Krampitz and Norton, 2014).

Familial medullary thyroid carcinomas (FMTC)

RET mutations in FMTC are gain-of-function mutations.

Disease

Medullary thyroid carcinomas (MTC) develop in either sporadic (75%) or hereditary form (25%). Familial Medullary thyroid carcinomas is an autosomal dominant syndrome of tumors of neuroendocrine origin that arise from para-follicular C cells which secrete a variety of peptides and hormones including calcitonin. FMTC can be an isolated condition, or part of MEN2A or MEN2B. It is caused by missense mutations in RET. Germline-activating RET mutations are found in 95%-98% of hereditary MTC, most often mutations in one of the 5 cysteines (aa 609, 611, 618, 620, exons 10 and aa

634, exon 11, cysteine-rich domain), mutations in aa 768, 790, 791, exon 14 or aa 804, 844 and aa 891, exon 15 being less frequent (in the tyrosine kinase domain). RET mutations are present in 25%-40% of sporadic MTC. Activating point mutations in RAS genes (HRAS, KRAS, and NRAS) has been described in RET-negative sporadic MTC. Patients with a RET mutation had a worse outcome. The most frequent mutation in sporadic MTC was RET M918T (from c.2753T>C). RET C634W (from c.1902C>G) was also found frequently (Ceolin et al, 2012; Somnay et al., 2012; Krampitz and Norton, 2014; Ciampi et al., 2019).

Familial pheochromocytoma predisposition

RET mutations in familial pheochromocytoma predisposition are gain-of-function mutations.

Disease

Pheochromocytomas are adrenal medullary tumors (while paragangliomas arise from extra-adrenal ganglial sympathetic/parasympathetic chains) secreting catechocatecholamines with tachycardia, sweating and hypertension. It is an inherited form of cancer (autosomal dominant syndrome) in 10% to 25% of cases.

In familial cases, pheochromocytoma is a component of one of the four following autosomal dominant syndromic diseases, Multiple Endocrine Neoplasia type 2, Von-Hippel-Lindau disease, hereditary paraganglioma syndrome and neurofibromatosis type 1. Pheochromocytoma is associated with germline and/or somatic mutations in more than 20 genes, mainly genes of the hypoxia-inducible factor (HIF) signaling pathway, succinate dehydrogenase genes and VHL, the kinase signaling pathway, including RET and RAS genes, and Wnt and Hedgehog pathways.

In 75 to 90% cases, it is a sporadic or a non-syndromic disease of an unknown etiology (Gimenez-Roqueplo 2003; Jochmanova and Pacak, 2018).

RET mutations in pheochromocytoma are mainly found in exons 10, 11, 13 and 16. Carriers of codon 634 germline mutations present with much younger mean age of onset, and have a higher risk of developing pheochromocytomas.

Hirschsprung disease

RET mutations in Hirschsprung disease are loss of function mutations.

Disease

Hirschsprung disease or aganglionic megacolon is an autosomal dominant syndrome characterized by congenital absence of ganglion cells of the gastrointestinal tract (deficit in enteric nervous system), due to defective neural crest cell development. More than 10 genes are known to be possibly implicated in this disease, including RET, SOX10, ZEB2, EDNRB, EDN3 and PHOX2B.

Expression and penetrance of a RET mutation is variable and sex dependent (penetrance is 70% in males and 50% in females). More than 80 mutations have been identified, in particular: S32L, Y36C, L40P, P64L, L72P, R77C, G93S, L123F, A143G, C197Y, R231H, D264K, R287K, D300K, D300N, F329FfsX24, R330Q, R330N, R360W, P399L, R418X, D469N, R475Q, C611G, C620Y, all in the extracellular region (Anders et al., 2001; Butler Tjaden et al., 2013; Plaza-Menacho, 2017; Lorente-Ros et al., in press).

Congenital central hypoventilation syndrome (CCHS)

RET mutations in CCHS are loss of function mutations.

Disease

Congenital central hypoventilation syndrome (also called Haddad syndrome, Ondine-Hirschsprung disease), is a life-threatening syndrome characterized by impaired ventilatory response to hypercarbia and hypoxemia, Hirschsprung disease and tumors of neural-crest derivatives. It is sporadic in the majority of cases, and autosomal dominant in other cases, implicating PHOX2B, RET, GDNF, ASCL1 or EDN3 (Bolk et al., 1996; Amiel et al., 2003).

Renal hypodysplasia/aplasia 1 (RHDA1)

RET mutations in RHDA1 are loss of function mutations.

Disease

Renal hypodysplasia/aplasia 1 is an autosomal recessive syndrome which usually results in death in utero or in the perinatal period, and is associated with 3 genes ITGA8, PAX2, and RET according to LOVD. About 5% of living patients with congenital anomalies of the kidneys or lower urinary tract harbor mutations in the RET pathway, and RET mutations are present in 30% of fetuses with unilateral or bilateral renal agenesis. RET mutations or other alteration of the RET signaling pathway provokes delayed attachment of Wolffian duct to reach the cloaca, delayed degeneration of the mesonephros, renal agenesis or cystic dysplastic kidneys and ureters (Davis et al., 2014).

Thyroid cancers

Disease

Thyroid cancer includes papillary thyroid carcinoma (PTC, 80% of thyroid cancers), follicular thyroid carcinoma (FTC, 10%-15% of thyroid cancers), medullary thyroid cancer (MTC, 5%-8% of thyroid cancers), and anaplastic thyroid cancer (less than 5%). Squamous and mucoepidermoid

carcinomas account for 1% and 0.5 % of thyroid carcinomas.
RET translocations/fusion genes have been described in 20-40% of patients with papillary thyroid carcinoma, with higher frequency in radiation-exposed patients and mutations in RET have been reported in 40-70% of patients with medullary thyroid carcinoma (Kato et al., 2017)

Oncogenesis
RET **polymorphisms** and thyroid cancer: G691S, L769L and S904S polymorphisms were associated with predisposition to the development of sporadic MTC (Ceolin et al, 2012).
Medullary thyroid cancer: Amplification: 30% of medullary thyroid carcinomas harbour RET gene amplification with no alterations in chromosome 10 or a polysomy of chromosome 10, in variable percentage of cells, suggesting cell heterogeneity. RET copy number alterations can be considered a poor prognostic factor potentiating the poor prognostic role of RET mutation (Ciampi et al., 2012). **Mutations:** The far most frequent mutation in medullary thyroid cancer is M918T. Other mutations are: D631_L633delinsE, D631_L633delinsA, E632_L633del, C634R (cBioPortal). ATF4 promotes RET degradation. Low ATF4 expression correlates with poor overall survival of patients with MTC (Bagheri-Yarmand et al. 2017).
Papillary thyroid cancer: The most common rearrangements are translocation/fusion gene t(10;10)(q11;q21) CCDC6/RET and fusion gene NCOA4/RET, accounting for about 90%. **Translocations/fusion genes** in papillary thyroid cancer: t(1;10)(p13;q11) TRIM33/RET, t(3;10)(q26;q11) TBL1XR1/RET, t(5;10)(q35;q11) SQSTM1/RET, t(6;10)(p22;q11) TRIM27/RET, t(7;10)(q33;q11) TRIM24/RET, t(7;10)(q34;q11) TAS2R38/RET, t(8;10)(p22;q11) PCM1/RET, t(8;10)(p11;q11) HOOK3/RET, t(9;10)(q32;q11) FKBP15/RET, t(10;10)(p14;q11) TAF3/RET, t(10;10)(p12,q11) ANKRD26/RET, t(10;10)(p12;q11) ACBD5/RET, t(10;10)(p11;q11) KIF5B/RET, t(10;11)(q11;p15) PPFIBP2/RET, NCOA4/RET (10q11), t(10;10)(q11;q21) ANK3/RET, t(10;10))(q11;q21) SLC16A9/RET, t(10;10)(q11;q21) CCDC6/RET, t(10;10)(q11;q21) RUFY2/RET, t(10;10)(q11;q25) AFAP1L2/RET, t(10;10)(q11;q26) CLRN3/RET, t(10;12)(q11;q13) ERC1/RET, t(10;14)(q11;q22) KTN1/RET, t(10;14)(q11;q32) GOLGA5/RET, t(10;15)(q11;q25) AKAP13/RET, t(10;17)(q11;p13) MYH13/RET, t(10;18)(q11;q21) RELCH/RET, t(10;22)(q11;q11) SPECC1L/RET (PMID 8634704, 10337992, 10439047, 10741739, 10850414, 10980597, 11156407, 16946010, 17639057, 25175022, 25204415, 25417114, 25500544, 25546157, 27683183, 28351223, 28911147, 30466862, 31425920, 31715421 and data from Atlas Band 10q11).
Poorly differentiated thyroid cancer: mutation A1105V was found, and also **translocations/fusion genes** t(3;10)(q12;q11)TFG/RET, t(3;10)(q26;q11) PDCD10/RET and t(10;10)(q11;q21) CCDC6/RET.

Lung cancers

Disease
Non-small cell lung carcinomas (NSCLC) are classified as: adenocarcinomas (30-40% of lung tumors), squamous cell carcinomas (40% of tumors), adenosquamous carcinomas, large cell carcinomas, sarcomatoid carcinomas, carcinoid tumors, and salivary gland tumors. Small cell lung carcinoma (SCLC), 20% of tumors, is a pulmonary neuroendocrine tumor. Other neuroendocrine tumors of the lungs are large cell neuroendocrine carcinomas, typical carcinoids, and atypical carcinoids.
RET translocations/fusion genes have been reported in 1% to 2% of patients with non-small cell lung cancer. Most cases of RET fusion-positive NSCLCs are adenocarcinoma, although Cai et al., 2013 screening 392 patients with NSCLC found 6 patients (1.5%) with a KIF5B/RET fusion: 4 had adenocarcinoma, 1 had a malignant neuroendocrine tumor, and 1 had squamous cell carcinoma. However, a meta-analysis of 165 patients with RET-rearranged NSCLC from 29 centers across Europe, Asia, and the United States was conducted. Median age was 61 years (range, 29 to 89 years). The majority of patients were never smokers (63%) with lung adenocarcinomas (98%); squamous cell (1%) and advanced disease (91%). The most frequent rearrangement was KIF5B/RET (72%); CCDC6/RET was found in 19 patients (23%), NCOA4/RET in two patients (2%), EPHA5/RET in one patient (1%), and PICALM/RET in one patient (1%) (Gautschi et al., 2017). In a study screening 1139 lung adenocarcinoma patients, ALK fusions were detected in 5.1% of cases, RET fusions in 1.3%, and ROS1 fusions in 1%. No significant difference in survival was observed between fusion-positive and fusion-negative patients (Pan el al., 2014). RET mutations in small-cell (neuroendocrine) lung cancer is extremely rare (Rudin et al., 2014).

Oncogenesis
Cells expressing oncogenic KIF5B/RET are sensitive to multi-kinase inhibitors that inhibit RET (Lipson et al., 2012).
A study on non-small-cell lung cancer showed RET **amplification** in 3%, low RET gene copy number gain in 8%, and RET over expression in 8% of cases (Platt et al., 2015).
RET **translocations/fusion genes** in NSCLC: t(1;10)(p13;q11) TRIM33/RET, t(2;10)(p21;q11) EML4/RET, t(2;10)(p16;q11) EML6/RET,

t(4;10)(q13;q11) APHA5/RET, t(6;10)(p22;q11) KIF13A/RET, t(6;10)(q22;q11) TBC1D32/RET, t(6;10)(q22;q11) PTPRK/RET, t(7;10)(q22,q11) CUX1/RET, t(7;10)(q33;q11) TRIM24/RET, t(8;10)(p22;q11) PCM1/RET, t(8;10)(p12;q11) RBPMS/RET, t(10;10)(p13;q11) CCDC3/RET, t(10;10)(p13;q11) PRPF18/RET, t(10;10)(p13;q11) FRMD4A/RET, t(10;10)(p12;q11) KIAA1217/RET, t(10;10)(p12;q11) WAC/RET, t(10;10)(p11;q11) PRKCQ/RET, t(10;10)(p11;q11) ARHGAP12/RET, t(10;10)(p11;q11), KIF5B/RET, t(10;10)(p11;q11) PARD3/RET, CCNYL2/RET (10q11), RASSF4/RET (10q11), NCOA4/RET (10q11), PRKG1/RET (10q11), t(10;10)(q11;q21) CCDC6/RET, t(10;10)(q11;q21) CTNNA3/RET, t(10;10)(q11;q21) SIRT1/RET, t(10;10)(q11;q21) RUFY2/RET, t(10;10)(q11;q23) DYDC1/RET, t(10;10)(q11;q24) SORBS1/RET, t(10;10)(q11;q25) ADD3/RET, t(10;10)(q11;q25) CCDC186/RET, t(10;10)(q11;q26) DOCK1/RET, t(10;11)(q11;q14) PICALM/RET, t(10;12)(q11;q13) ERC1/RET, t(10;12)(q11;q23) ANKS1B/RET, t(10;12)(q11;q24) CLIP1/RET, t(10;14)(q11;q12) TSSK4/RET, t(10;14)(q11;q32) CCDC88C/RET, t(10;15)(q11;q21) MYO5C/RET, t(10;17)(q11;p11) MPRIP/RET, t(10;17)(q11;q24) PRKAR1A/RET, t(10;18)(q11;q21) KIAA1468/RET, t(10;19)(q11;q13) LSM14A/RET (PMID 22327623, 23150706, 23533264, 27150058, 28115111, 28851076, 29571998, 29935851, 30429449, 30579554, 32127187, 32216946, Ignatius Ou and Zhu, in press, and data from Atlas Band 10q11).

mutations in lung adenocarcinoma: L56M, E61K, T75K, R77C, R77L, H103N, L109I, X113_splice, K124*, E164K, P181H, E251Q, D290N, R297L, T350N, H352P, R355M, Q371K, V374M, L375Q, S406R, X421_splice, E428G, G453W, D460V, A479S, M484T, R494M, A496G, G506W, A510S, A513E, C541F, P560H, P566T, D567Y, X587_splice, G588D, G593R, C611S, V648I, F719L, P720L, V739F, V755L, V757M, M759I, N763K, P766Q, L790*, G798V, A807P, R817H, D839N, M848V, Q860P, S891*, E901K, S932N, E978Q, E1006*, M1009K, R1013K, D1031Y, L1048Pfs*11, E1072K, dispersed through all the RET length.

mutations in lung squamous cell carcinoma, according to cBioPortal: R33Kfs*29, A59S, R114S, R114H, E235Q, M255I, W324C, E366*, S462L, E530*, T564N, G691Vfs*40, A756G, E775Sfs*5, F776S, G825C, W856L, W917R, A919S, V934=, W942S, P951S, E979Q, R1013T, V1095.

Breast carcinoma

The treatment-relevant subtypes of invasive carcinoma are based on "ER" (estrogen receptors ESR1 and ESR2), "PR" (progesterone receptor PGR) and "HER2" (ERBB2) status: ER+, ER-, PR+, PR-, HER2+, HER2-. Last, ER-/PR-/HER2- are called basal-like or triple negative breast cacinoma.

Oncogenesis

Tumor-specific expression of GDNF and ARTN is relatively frequent and can promote autocrine activation of RET downstream signaling. RET is an estrogen receptor target gene. IL6 and RET form a positive feed-forward loop that stimulates migration. ET activation increases migration and proliferation of ER+ (estrogen receptor +) breast cancer. Elevated RET levels are found not only in ER+ tumors, but in other sub-types of human breast cancer and correlate with decreased metastasis-free survival and poor prognosis in breast cancer patients. RET alterations (amplifications/copy number gains, mutations or chromosome rearrangements) were found in 1.2% in a large cohort of 9693 breast cancers. RET amplifications were the most commonly observed and mainly found in ER- and HER2- breast cancers, followed by missense mutations and rearrangements. RET missense mutations were more frequently associated with ER+ breast cancers. NCOA4/RET positive breast cancer responds to cabozantinib. Expression is higher in recurrent cancers and is correlated with larger tumor size, higher tumor stage and reduced metastasis-free and overall survival. RET expression in breast cancer is also correlated with resistance to endocrine therapies via stimulation of the PI3K/AKT/MTOR signaling pathway. Tyrosine kinase inhibitors could be useful treatments (Gattelli et al., 2013; Morandi et al., 2013; Hatem et al., 2016; Paratala et al., 2018; Mulligan 2019).

RET **mutations:** P117T, S148del, F195L, R330Q, R368C, A479T, P537Qfs*101, S518C, A604D, C611Y, I625M, C634R/G, F663Lfs*12, V778I, A793Pfs*76, G828A, D842H, L846I, I852M, M868I, M918T, P951Lfs*12, X934_splice L963V, E991*, L1101V, dispersed through all the RET length (cBioPortal); and **translocations/fusion genes:** t(10;12)(q11;q13) ERC1/RET, NCOA4/RET (10q11), RASGEF1A/RET (10q11) (Stransky et al., 2014; Paratala et al., 208; Rich et al., 2019).

Epithelial ovarian cancer.

Oncogenesis

Genomic RET missense mutations was found in 2% of patients. These **mutations** were: D58N, R114H, R205S; G248S; A342G, T636M, A680T, G727V, G751V, K780N, N879S, N879D, N879S, X934_splice, R959W, A1105G, and K1107N. Patients with RET alterations had shorter progression-free survival than those without RET alterations. R693H and A750T mutants of RET enhance the signal transduction of RET, the cell viability and colony formation of cells, and the

growth of tumor xenografts of ovarian cancer (Guan et al., 2020). **Translocations/fusion gene:** NCOA4/RET fusion was found in an ovarian germ cell tumour. As a matter of fact, it was a papillary thyroid carcinoma arising in struma ovarii (struma ovarii originate from ovarian germ cells) (Richardson and Mulligan, 2009). KIF5B/RET and CCDC6/RET fusion genes were also found (Kato et al., 2017; Gao et al., 2018).

Uterine endometrioid carcinoma

Endometrioid carcinoma is the most common endometrial cancer (75%), and endometrial carcinoma represents 95% of uterine corpus cancers. It is an epithelial neoplasia.

Oncogenesis

Mutations G115S, R133C, K161E, R180*, L196S, C197Y, T225M, A241V, E251K, P273T, R313W, T317M, R330Q, R348Q, A349V, A373V, A386V, S396L, R418*, I422=, T451M, R474W, A487V, E511D, V573M, P596H, E623K, A640V, S649L, I657S, A672S, A680T, R721W, E768G, A793D, R844Q, I858V, S891L, R912W, S936Y, R969W, C976Y, E978D, R982H, A999V, E1006D, L1018I, A1019V, G1063D, X1063_splice, N1092H, L1108*, D1110G, dispersed through all the RET length. RET **high expression** is an unfavorable prognostic marker in endometrial cancer (The Human Protein Atlas).

Colorectal cancer

Disease

RET fusions have been described in less than 1% of colorectal cancers.

Oncogenesis

A study on 37 cases determined 4 cases with RET mutations/variants: R77C, P270L, G533C, P1047S. RET activating mutations identified in colon cancer patients increase anchorage-dependent cell proliferation and clonogenic cell survival. Variant G533C is clearly oncogenic whereas RET variant P1047S is not. Cells expressing the RET G533C mutant are sensitive to treatment with the RET specific inhibitor vandetanib (Mendes Oliveira et al., 2018). RET fusions were more frequent in older patients, right-sided tumors, MSI-high, RAS and BRAF wild-type. Patients with RET fusion-positive tumors showed a significantly worse overall survival (Pietrantonio et al., 2018). The following RET **mutations** were found: A4E, T48M, G74S, R77H, R79W, F126C, R133H, R175H, R177W, E235G, V245M, V260*, K288N, A306V, G321R, T328S, R360Q, A373V, R418*, R418Q, A432V, T451M, Y508H, E511K, R525W, X550_splice, D571N, E595K, Q703H, V706M, X712_splice, P715S, T742M, T754M, A756V, R770*, K789E, R817C, M848V, Q860R, E867A, R912W, P914S, P951A, R959W, T1022A, L1016F, T1055A (cBioPortal) and **translocations/fusion genes** were: NCOA4/RET (10q11), t(5;10)(q33;q11) TNIP1/RET, t(7;10)(q34;q11) TRIM24/RET, t(10;10)(q11;q21) CCDC6/RET, t(10;19)(q11;q13) SNRNP70/RET and t(10;20)(q11;p12) RRBP1/RET (Stransky et al., 2014; Le Rolle et al., 2015; Kloosterman et al., 2017; Pietrantonio et al., 2018).

Aberrant methylation of RET is found in colon adenomas and adenocarcinomas, and is associated with decreased RET expression, potentially leading to inhibition of RET-induced apoptosis of colon cancer cells (Li et al., 2019).

Esophageal adenocarcinoma

Oncogenesis

Mutations E61K, Q187K, E238K, C565F, P582L, M848I, A1019V.

Gastric adenocarcinoma

Oncogenesis

Mutations G69D, R205G, A279T, R287W, R313W, A349V, A432V, N448S, T451M, F466S, Q583*, P613L, V706M, R721Q, A793T, R817H, R820H, R833C, K907T, E921D, N950Tfs*15, E978K, M1009V, N1045S, A1046T. **Fusion gene:** CCDC6/RET.

Pancreatic ductal adenocarcinoma

Oncogenesis

The common **polymorphic variant** G691S (polymorphism found in 30% of normal pancreas, allelic frequency of 15%) is over represented in pancreatic ductal adenocarcinomas patients (allelic frequency of 20%)

Overexpression of G691S RET increased invasion of pancreatic cancer cells (Sawai et al., 2005). Activation of RET is capable of inducing invasive pancreatic carcinomas. RET **mutations** in pancreatic carcinomas, according to cBioPortal are: A4V, R57W, R57Q, V276I, F329L, A756D, R844W, R770*, R897*, P1070S.

Leukemias

Oncogenesis

RET expression in acute myeloid leukemia is maturation-associated: RET gene expression occurs more frequently in AMLs displaying either a monocytic (M4/M5) or intermediate-mature myeloid phenotype (M2/M3) than in leukemias reflecting an earlier stage of myeloid differentiation (M0/M1). (Gattei et al., 1998).

The following RET **mutations** found in leukemias were: G691S in acute myeloid leukemia, G691S, R982C in B-lymphoblastic leukemia, L816P in T-lymphoblastic leukemia, N336T in diffuse large B-cell lymphoma, G115S in mature B-cell neoplasm NOS, X587_splice in angioimmunoblastic T-cell lymphoma, G691S in peripheral T-cell lymphoma

NOS (BioPortal). and the following **translocations:** a t(6;10)(q27;q11) FGFR1OP/RET and a t(10;22)(q11;q11) BCR/RET were found in chronic myelomonocytic leukemia and in primary myelofibrosis with secondary acute myeloid leukemia, and a t(9;10)(q32;q11) FKBP15/RET in acute myeloid leukemia NOS (Ballerini et al., 2012; Bossi et al., 2014; Gao et al., 2018).

Bladder urothelial carcinoma

Oncogenesis

Mutations V245A, E337K, R348Q, E673K, R817C, E818D, E884K, G949Efs*16, F998L, A999E, M1009I, N1059D, D1081H, M1109I.

Papillary renal cell carcinoma

Oncogenesis

Cytoplasmic and nuclear expression of RET are strong negative predictors of survival in papillary renal cell carcinoma (Li et al., 2019).

Nervous system tumors

Oncogenesis

Astrocytoma: **Mutations** G47S, P182S, G435D, A807T, R813W, D1093G.

Glioblastoma multiforme: **Mutations** N113=, R133H, R133C, R171K, D219N, E289A, S339*, N361I, N437I, G546R, R635H, A682V, D892N.

Neuroblastoma (Peripheral neuroblastic tumours of the sympathetic nervous system, mainly found in infants and young children): RET was found to be highly expressed (Li et al., 2019).

Head and neck squamous cell carcinoma

Oncogenesis

Mutations Q44H, V63M, N84S, E284Q, E337V, E366*, A373V, A386T, Y483D, C585S, E616del, C634Y, K740N, T946A.

Salivary glands tumors

Oncogenesis

t(6;10)(p22;q11) TRIM27/RET, NCOA4/RET fusion and t(10;12)(q11;p13) ETV6/RET were found in intraductal carcinoma, invasive carcinoma and secretory carcinoma of the salivary glands (Skálová et al., 2018a; (Skálová et al., 2018b; Guilmette et al., 2018; Skálová et al., 2019).

Prostate cancer

Oncogenesis

RET is expressed in prostate cancer cell lines established from advanced prostate cancers. RET is also expressed in about 20% of localized prostate adenocarcinomas as well as in small cell neuroendocrine cancers of the prostate. GDNF is expressed by nerves, and nerve fibers secrete GDNF in the peritumoral stroma in prostate cancer. GDNF/RET signaling can enhance proliferation, invasion in prostate cancers (Ban et al. 2017). RET was overexpressed in patients with neuroendocrine prostate cancer (VanDeusen et al. in press). The following **RET mutations** were found: R57W, R67C, T130I, V202M, A281T, V782I, R886W, A1046S and **translocations/fusion genes** were: NCOA4/RET fusion (cBioPortal).

Skin neoplasms

Oncogenesis

RET G691S **polymorphism** is frequent in skin melanoma (found in 30% of the cases), particularly in desmoplastic subtypes (6%), compared to the general population (15-20%). The polymorphism was germline in 30% of the patients with desmoplastic melanomas and 21% of the patients with non-desmoplastic melanoma. RET G691S may be a genetic risk factor for the development of desmoplastic melanoma (Narita et al., 2009; Barr et al., 2012).

Mutations in **squamous cell carcinoma**: X25_splice, W85*, E107K, R114H, T120S, D547G, P599S, S705F, G736E, Y826F, Y826*, E843K, R844W, P957L.

Mutations in **skin melanoma** are the following: X25_splice, A55V, E62K, R67C, W85*, T92I, G141S, P155S, E208D, P259Q, X290_splice, G308V, E309K, P320S, D322N, W324L, E337K, A342V, E366Q, N367S, S379*, R417C, A472V, E480K, L481R, D627N, V685I, S696*, D698N, W717*, G736R, A741T, F744Y, H745N, G823ED839N, P841S, L851I, R873W, R897P, K907N, R912Q, S936F, M970I, D1000N, G1032D, E1036Q, P1049S, E1058K, D1093N, L1108* (cBioPortal).

Translocations in **melanomas/ Spitz tumors** were: t(10;10)(p11;q11) KIF5B/RET and t(10;14)(q11;q32) GOLGA5/RET (Wiesner et al., 2014).

Soft tissue sarcomas

Disease

A t(7;10)(q11;q11) CLIP2/RET, a t(10;10)(p12;q11) KIAA1217/RET, and a t(10;17)(q11;p13) MYH10/RET were found in spindle mesenchymal neoplasms (Davis et al., 2020). A t(3;10)(q12;q11) TFG/RET and NCOA4/RET (10q11) were found in spindle cell tumors (Michal et al., 2019; Loong et al., 2020). A t(10;22)(q11;q12) TIMP3/RET was found in an inflammatory myofibroblastic tumor of the uterus (Cheek et al., 2020). A t(10;17)(q11;p13) MYH10/RET was found in an infantile myofibromatosis (Rosenzweig et al., 2017). A t(1;10)(q25;q11) RASAL2/RET was found in high-grade sarcoma (Zhou et al., 2020).

Pediatric cancers

RET gene fusions have been reported in 20% to 45% of papillary thyroid carcinomas and less frequently in pediatric and young adult patients with glioma and various pediatric soft tissue tumors. CSGALNACT2/RET fusion gene was found in a paediatric high grade glioma (Carvalho et al., 2014).

A VCL/RET fusion gene was found in 7 year-old boy with lipofibromatosis, a rare pediatric soft tissue tumor (Al-Ibraheemi et al., 2019). Ortiz et al., 2020 described 5 patients: 2 cases of medullary thyroid cancer, aged 7yrs and 15yrs with RET mutation; a 7mth-old baby with infantile myofibroma/hemangiopericytoma and a MYH10/RET fusion gene; a 2mth-old baby with mesoblastic nephroma / infantile fibrosarcoma and a SPECC1L/RET fusion gene; and a case of lipofibromatosis presenting at birth with a NCOA4/RET fusion. Infantile myofibromatosis may also harbour RET chromosomal rearrangements see above).

Breakpoints

Note

In a series of from 32,989 advanced cancers twenty-five different breakpoint combinations were observed, >95% of which involved intron 11 of RET, most commonly fused with intron 15 of KIF5B in 80%, intron 1 of CCDC6 in 90%, or intron 8 or 10 of NCOA4 in 36 and 57% respectively. KIF5B/RET translocations were highly specific for non-small cell lung carcinoma (Rich et al., 2019). Santoro et al., 2020 present a lovely representative scheme of RET and 50 fusion partners, indicating the most frequent breakpoint sites in partner proteins, and their domains retained in the fusion protein.

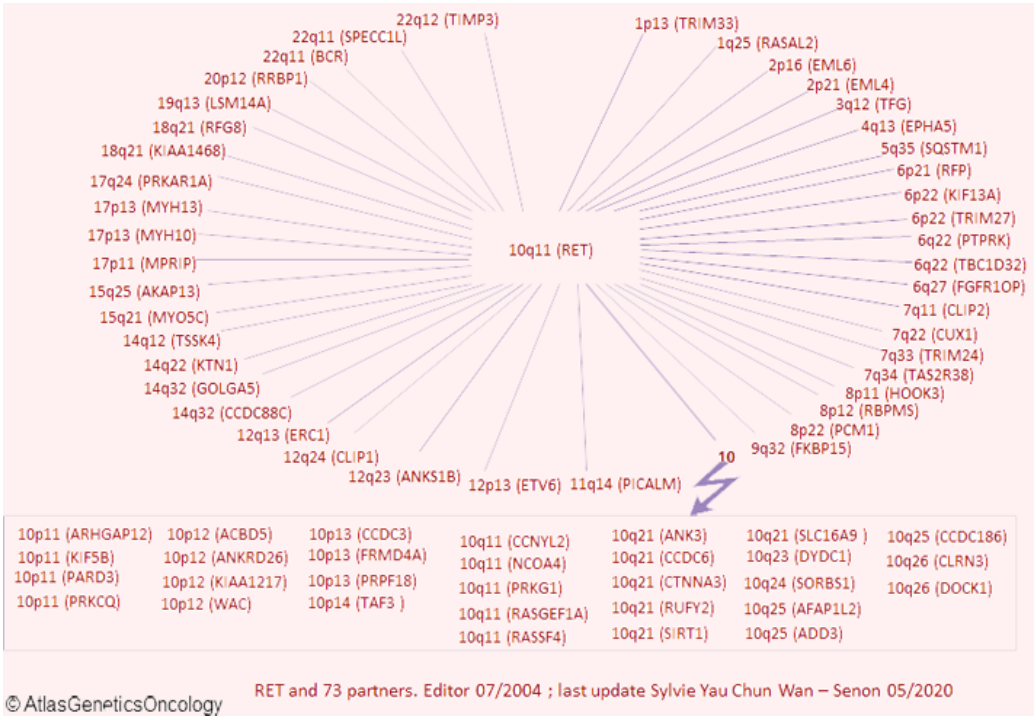

Figure 6: RET Partners

Hybrid Gene	Partner Gene	Last Exon	Breakpoint	RET	RET First Exon	Breakpoint	Tissue
TRIM33/RET	5' TRIM33	16	1_2976	3' RET	12	2369_5659	Thyroid (0.7%)
TRIM27/RET	5' TRIM27	3	1_1104+6742	3' RET	12	2369-1668_5659	Thyroid (1.4%)
TRIM24/RET	5' TRIM24	9	1_1745	3' RET	12	2369_5659	Thyroid (0.7%)
PCM1/RET	5' PCM1	29	1_5266	3' RET	12	2369_5659	Thyroid (1.8%)
HOOK3/RET	5' HOOK3	11	1_1322	3' RET	12	2369_5659	Thyroid (1.8%)
KIF5B/RET	5' KIF5B	15	1_2183	3' RET	12	2369_5659	
	5' KIF5B	16	1_2372	3' RET	12	2369_5659	Skin 2.6%; Lung (1.5%)
NCOA4/RET	5' NCOA4	8	1_907	3' RET	12	2369_5659	Thyroid (8%), Lung, Soft tissue

CCDC6/RET	5' CCDC6	1	1_535	3' RET	12	2369_5659	Thyroid (12.7%;) Lung 50.5%
ERC1/RET	5' ERC1	11	1_2338	3' RET	12	2369_5659	Thyroid (1%)
KTN1/RET	5' KTN1	29	1_2960	3' RET	12	2369_5659	Thyroid (1.4%)
GOLGA5/RET	5' GOLGA5	7	1_1747	3' RET	12	2369_5659	Skin (2.6%); Thyroid (0.8%)
PRKAR1A/RET	5' PRKAR1A	7	1_825	3' RET	12	2369_5659	Thyroid (2.7%)
RELCH/RET	5' RELCH	10	1_1852	3' RET	12	2369_5659	Lung (0.2%)

TABLE 2: Breakpoints according to Cosmic

1p13 TRIM33/RET PMID 10439047, 11786418, 14668719

6p22 TRIM27/RET PMID 12787916, 14668719

7q33 TRIM24/RET PMID 10439047, 11786418, 14668719

8p22 PCM1/RET PMID 10980597, 14668719

8p11 HOOK3/RET PMID 14668719, 17639057

10p11 KIF5B/RET PMID 22194472, 22327622, 22327623, 22327624, 22797671, 23150706, 23418494, 23891510, 24133367, 24158231, 24346091, 24445538, 24469108, 24481316, 24700479, 24722163, 24727320, 24810493, 25348872

10q11 NCOA4/RET PMID 8180971, 8187085, 8290261, 8545102, 8806699, 8806700, 9001272, 9466701, 9482114, 9516913, 9528832, 9669285, 9935226, 10083732, 10675479, 10720057, 10773666, 10946873, 11117781111117782, 11443191, 11747322, 11786418, 11788677, 11927965, 12057919, 12720532, ,, 14668719, 15737050, 15788648, 15876154, 16015630, 16595592, 16784981, 17464312, 17727338, 17786355, 18226854, 18393128, 18757433, 19495791, 19958951, 20012784, 20099311, 20447069, 20564403, 20703476, 20712653, 20840674, 20924280, 21048359, 21173509, 21219595, 21411555, 21498916, 22481925, 22682753, 22745248, 22895275, 22961909, 23150706, 23436219, 23806056, 23966419, 24277231, 24417340, 24503805, 24613930, 24915144, 25111330, 26971368

10q21 CCDC6/RET PMID 2406025, 8545102, 8634704, 9001272, 9466701, 9508203, 9516913, 9528832, 9669285, 9935226, 10083732, 10675479, 10720057, 10773666, 10931090, 10946873, 10951397, 11117781, 11117782, 11443191, 11493988, 11747322, 11786418, 11788677, 11927965, 12057919, 12720532, 14668719, 15737050, 15788648, 15876154, 16015630, 16595592, 16784981, 17464312, 17727338, 17786355, 18226854, 18393128, 18757433, 19055826, 19495791, 19958951, 20012784, 20099311, 20447069, 20564403, 20703476, 20712653, 20840674, 20924280, 21048359, 21173509, 21219595, 21411555, 21498916, 22327623,22481925,22682753, 22745248, 22895275, 22961909, 23150706, 23436219, 23806056, 23966419, 24133367, 24158231, 24277231, 24327398, 24346091, 24417340, 24469108, 24503805, 24613930, 24700479, 24727320, 24810493, 24915144, 25111330, 25348872, 26187428, 26971368, 27588476

12q13 ERC1/RET PMID 10337992, 14668719, 15876154

14q22 KTN1/RET PMID 10850414, 11786418, 14668719, 18757433

14q32 GOLGA5/RET PMID 9443391, 10675479, 10773666, 11786418, 14668719, 24445538

17q24 PRKAR1A/RET PMID 7519046, 7678053, 8545102, 9466701, 9516913, 9528832, 9669285, 9935226, 10083732, 10675479, 10720057, 10773666, 10946873, 11117781, 11117782, 11747322, 11786418, 11788677, 14668719, 15876154, 18393128, 20447069, 22481925, 24277231

18q21 RELCH/RET PMID 24727320

To be noted

Treatments with RET inhibitors are promising therapeutic targets.

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