## Phylogeny

• Orthologs have been identified across all vertebrate classes and in the cephalochordate Amphioxus; an enzymatically active orthologue exists in Drosophila melanogaster despite lacking GDNF ligands (ibanez2013structureandphysiology pages 2-4).  
• The cytoplasmic domain is ~90 % identical among vertebrates, underscoring strong evolutionary pressure (knowles2006structureandchemical pages 1-2).  
• Within the human kinome, RET is placed in the Tyrosine Kinase (TK) group, receptor tyrosine kinase family, and clusters phylogenetically with the FGFR/VEGFR sub-families (roskoski2018roleofret pages 2-3).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (knowles2006structureandchemical pages 11-12, roskoski2018roleofret pages 5-6).

## Cofactor Requirements

Catalytic turnover is strictly Mg²⁺-dependent, as shown in biochemical assays using Mg²⁺-ATP (knowles2006structureandchemical pages 5-6, roskoski2018roleofret pages 6-7).

## Substrate Specificity

• Efficiently phosphorylates acidic substrates such as poly(E₄Y), indicating preference for acidic residues N-terminal to the acceptor Tyr (knowles2006structureandchemical pages 4-5).  
• Autophosphorylation targets include Y687/Y697 (juxtamembrane), Y900/Y905 (activation loop), and Y1062 (C-terminal tail) (roskoski2018roleofret pages 6-7).  
• The MEN2B mutant M918T reprograms specificity, favouring STAT3 over canonical substrates (knowles2006structureandchemical pages 2-2).

## Structure

• Domain architecture: four cadherin-like domains (CLD1-4), a cysteine-rich region, single transmembrane helix, juxtamembrane segment, and a split kinase domain containing a 15-residue insert (ibanez2013structureandphysiology pages 2-4, roskoski2018roleofret pages 5-6).  
• Crystal structures of the kinase domain are available (PDB 2IVT, 6Q2H, 7CRH) and reveal an active conformation irrespective of phosphorylation state (salvatore2021theimportanceof pages 21-23).  
• Catalytic core: Gly-rich loop (GxGxFG), Lys758–Glu775 salt bridge maintaining αC-in, HRDLAARN catalytic loop with Asp874 as general base, DFG-in motif, and gatekeeper Val804 controlling the hydrophobic pocket (knowles2006structureandchemical pages 6-7).  
• Regulatory elements: an N-terminal helix (res 705-711) tethers αC; regulatory and catalytic spines remain pre-aligned, accounting for modest structural change upon activation loop phosphorylation (knowles2006structureandchemical pages 6-7, knowles2006structureandchemical pages 7-7).  
• Inhibitor complexes: PP1 and ZD6474 bind in the ATP pocket engaging Val804; solvent-front residue G810 and Leu730 determine affinity for nintedanib, rationalising resistance mutations (knowles2006structureandchemical pages 7-7, terzyan2019structuralbasisof pages 1-1).

## Regulation

Post-translational modifications  
• Autophosphorylation of Y900/Y905 increases k\_cat approximately four-fold; Y905 is stabilised by Arg770, Arg897 and Lys907 (knowles2006structureandchemical pages 5-6).  
• Additional phosphosites: Y687, Y697, dual-specificity site S909, and docking residue Y1062 (roskoski2018roleofret pages 6-7).  
• N-linked glycosylation within the extracellular domain governs folding and surface expression (fancelli2021chasingthetarget pages 16-18).  
• Activated RET is poly-ubiquitinated by the CBL E3 ligase, promoting endocytosis and degradation (salvatore2021theimportanceof pages 28-32).

Allosteric / conformational control  
• Physiological activation requires ligand-bound GFRα co-receptor–mediated dimerisation; pathogenic C634R triggers ligand-independent disulfide-linked dimers, whereas M918T produces monomeric activation independent of Y905 phosphorylation (roskoski2018roleofret pages 12-13, knowles2006structureandchemical pages 7-9).

## Function

• Expression is high during embryogenesis in neural crest derivatives, kidney, and hematopoietic progenitors, with restricted adult expression in thyroid C-cells and select neuronal populations (fancelli2021chasingthetarget pages 1-2, roskoski2018roleofret pages 2-3).  
• Upstream ligands: GDNF, NRTN, ARTN, PSPN, and GDF15 bind GFRA1-4 or GFRAL, assembling a hexameric complex that brings two RET molecules together (roskoski2018roleofret pages 2-3).  
• Downstream signalling: phosphorylated RET recruits SHC and GRB2 to drive RAS-MAPK, PI3K to activate AKT, PLCγ to activate PKC, and SRC/JAK-STAT modules, thereby controlling proliferation, survival, migration and differentiation (fancelli2021chasingthetarget pages 1-2, desilets2023retalteredcancers—atumoragnostic pages 2-4).

## Inhibitors

• Multikinase inhibitors with clinical activity: vandetanib, cabozantinib, sorafenib, lenvatinib, sunitinib, ponatinib (roskoski2018roleofret pages 2-3, roskoski2018roleofret pages 12-13).  
• First-generation selective RET inhibitors: selpercatinib and pralsetinib, both FDA-approved for RET-altered thyroid and lung cancers (fancelli2021chasingthetarget pages 1-2, vodopivec2022retkinaseinhibitors pages 1-2).  
• Resistance mutations: gatekeeper V804L/M reduce ZD6474 binding (knowles2006structureandchemical pages 2-2); solvent-front G810A/S and hydrophobic core L730V or L881V impair vandetanib yet retain nintedanib sensitivity (terzyan2019structuralbasisof pages 1-1).

## Other Comments

• Activating mutations drive MEN2A (extracellular cysteine substitutions such as C634R) and MEN2B (M918T); loss-of-function mutations cause Hirschsprung disease (arighi2005rettyrosinekinase pages 1-2).  
• Oncogenic fusions—KIF5B-RET, CCDC6-RET, NCOA4-RET—constitutively activate the kinase in papillary thyroid carcinoma and non-small-cell lung cancer (roskoski2018roleofret pages 4-5, santoro2020retgenefusions pages 1-3).  
• Recurrent therapy-induced resistance cluster comprises V804, G810, L730 and L881 within the gate and solvent-front regions of the kinase domain (knowles2006structureandchemical pages 2-2, terzyan2019structuralbasisof pages 1-1).

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