## Phylogeny

• Member of the receptor tyrosine kinase (RTK) group, insulin-receptor family, ALK/LTK sub-family as classified in kinome surveys that follow Manning 2002 (unknownauthors2015diversityofreceptor pages 51-56).  
• The cytoplasmic kinase domain shares ~79 % amino-acid identity with Anaplastic Lymphoma Kinase (ALK), indicating a recent gene-duplication event (centonze2019ltkisan pages 15-18).  
• Mammalian LTK has lost the N-terminal MAM and LDLa modules retained in non-mammalian orthologs, whereas the TNF-like (TG) and EGF-like segments remain conserved (katic2023multifacetedrolesof pages 1-2).  
• Verified orthologs: Homo sapiens, Mus musculus, Danio rerio, Xenopus tropicalis and Gallus gallus (centonze2019ltkisan pages 15-18).

## Reaction Catalyzed

protein-L-tyrosine + ATP ⇄ protein-L-tyrosine-phosphate + ADP + H⁺ (roll2012alkactivatinghomologousmutations pages 1-2).

## Cofactor Requirements

No dedicated biochemical study is available; reviews note that, consistent with other RTKs, activity is presumed to require Mg²⁺ or Mn²⁺ (nadendla2025tyrosinekinasesstructural pages 18-19, farhan2020tyrosinekinasesignaling pages 4-6).

## Substrate Specificity

• Position-scanning peptide libraries assign LTK to a tyrosine-kinase class preferring acidic residues at −3/−1 and a hydrophobic residue at +1 around the target Tyr (nadendla2025tyrosinekinasesstructural pages 18-19).  
• Displays strong bias toward phosphorylating the first Tyr in Y-x-x-x-Y-Y motifs, consistent with data from cellular substrates (roll2012alkactivatinghomologousmutations pages 12-13).  
• Confirmed cellular substrate: Sec12 phosphorylated at Y10 and Y177, regulating COPII vesicle formation (centonze2019ltkisan pages 18-20).

## Structure

• Domain organization: signal peptide 1-16 – extracellular TG supradomain (TNF-like + glycine-rich) 17-424 – single transmembrane helix 425-449 – cytoplasmic kinase domain 450-864 (unknownauthors2023subcellularlocalizationand pages 12-15).  
• Crystal structure of the ectodomain (PDB 7NX1) reveals a composite TG fold with pGII helices forming the ligand-binding surface (munck2021structuralbasisof pages 13-17).  
• Catalytic core contains canonical VAIK (K567), HRD (H648-R650-D651) and DFG (D666-F667-G668) motifs; autophosphorylation occurs at Y672 within the activation loop (unknownauthors2023subcellularlocalizationand pages 39-44).  
• Active-state stabilisation mutations F568L (αC helix) and R669Q (DFG+1) map adjacent to regulatory motifs (roll2012alkactivatinghomologousmutations pages 12-13).  
• AlphaFold model AF-P29376 corroborates an intact regulatory and catalytic spine typical of active RTKs (unknownauthors2023subcellularlocalizationand pages 12-15).

## Regulation

• Autophosphorylation on Y672 is required for full catalytic activity and is detected predominantly at the Golgi apparatus (unknownauthors2023subcellularlocalizationand pages 39-44).  
• N-glycosylation at N257, N380 and N412 modulates receptor maturation, Golgi localisation and responsiveness to ligand; a N257Q/N380Q/N412Q triple mutant abolishes FAM150A-induced activation (unknownauthors2023subcellularlocalizationand pages 39-44).  
• Extracellular ligands FAM150A (Augmentor-β) and FAM150B (Augmentor-α) induce receptor dimerisation and kinase activation (zhang2014deorphanizationofthe pages 1-2, unknownauthors2023subcellularlocalizationand pages 12-15).  
• Ubiquitination by the E3 ligase CBL has been reported to regulate receptor turnover (nadendla2025tyrosinekinasesstructural pages 18-19).  
• Spatial regulation: activation requires an intact Golgi; Brefeldin A or FLI-06 disrupt activation by blocking Golgi integrity or ER export (unknownauthors2023subcellularlocalizationand pages 50-54).

## Function

• Expression: high in pre-B/B lymphocytes, brain, placenta and plasmacytoid dendritic cells (roll2012alkactivatinghomologousmutations pages 1-2, zhang2014deorphanizationofthe pages 3-4).  
• Interacting partners and substrates: Sec12 (direct phosphorylation) (centonze2019ltkisan pages 18-20); ERGIC-53 (stable complex) (unknownauthors2023subcellularlocalizationand pages 24-30); adaptor proteins IRS-1, Shc and PI3K bind NPXY motifs Y485/Y862 and Y753 respectively (unknownauthors2023subcellularlocalizationand pages 12-15).  
• Downstream signalling: activates MAPK, PI3K/AKT and JAK/STAT cascades in response to ligand binding or activating mutations (roll2012alkactivatinghomologousmutations pages 13-14, unknownauthors2023subcellularlocalizationand pages 15-20).  
• Cellular role: phosphorylation of Sec12 increases COPII budding, expanding ER exit-site number and accelerating ER-to-Golgi transport (centonze2019ltkisan pages 1-4).

## Inhibitors

• Crizotinib inhibits wild-type and F568L-mutant LTK, suppressing STAT5, AKT and ERK signalling and blocking soft-agar colony growth (roll2012alkactivatinghomologousmutations pages 13-14).  
• Ceritinib and Alectinib block autophosphorylation and impair secretory-pathway functions at 1 µM in cell-based assays (centonze2019ltkisan pages 15-18, unknownauthors2023subcellularlocalizationand pages 15-20).

## Other Comments

• Disease associations: over-expression or activating mutations linked to acute myeloid leukaemia and increased metastatic risk in non-small-cell lung cancer (nadendla2025tyrosinekinasesstructural pages 18-19).  
• Gain-of-function polymorphism near the PI3K-binding site enhances B-cell activation and predisposes to systemic lupus erythematosus (unknownauthors2023subcellularlocalizationand pages 15-20).  
• Catalogue of oncogenic mutations includes F568L, R669Q, P116S, G310E, A432T, V480I, R608*, Y616* and Q717K identified in lung cancers; many cluster near catalytic motifs and enhance kinase activity (roll2012alkactivatinghomologousmutations pages 12-13, palmer2015thealkreceptor pages 15-18).

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