## Phylogeny

• Tyrosine-protein kinase FRK belongs to the BRK/FRK/SRMS sub-family of atypical Src-related non-receptor tyrosine kinases positioned within the Tyrosine Kinase (TK) group of the human kinome (berndt2021newstructuralperspectives pages 1-2).  
• Orthologs: mouse Bsk/Iyk, rat Gtk and mouse Gtk (≈89 % identity), all highly conserved across mammals (unknownauthors2015effectsoffynrelated pages 31-35).  
• Shares ~49 % amino-acid identity with canonical SFK member Fyn and ~30–40 % identity with typical Src kinases, reflecting divergence after the Src lineage split (goel2016understandingthecellular pages 1-2, unknownauthors2015effectsoffynrelated pages 26-31).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-O⁴-phospho-L-tyrosine (unknownauthors2015effectsoffynrelated pages 14-18).

## Cofactor Requirements

Catalysis is Mg²⁺-dependent as shown for recombinant human FRK kinase preparations (yang2010asilentmutation pages 3-4).

## Substrate Specificity

• Validated physiological sites: PTEN Tyr336, EGFR Tyr1173, BRCA1 Tyr1152 (unknownauthors2022theroleof pages 37-42, goel2016understandingthecellular pages 6-8).  
• A global phosphopeptide consensus motif has not been defined in current literature (goel2016understandingthecellular pages 5-6).

## Structure

• Domain organisation: SH3 (residues 42-110), SH2 with bipartite NLS KRLDEGGFFLTRRR (116-208), bilobed kinase domain (234-491), C-terminal regulatory tail ending at Tyr497 (unknownauthors2015effectsoffynrelated pages 31-35).  
• Catalytic/regulatory residues: Lys262 (ATP anchoring), Asp351 (HRD motif), Tyr387 (activation-loop autophosphorylation), Tyr497 (inhibitory tail) (unknownauthors2015theroleand pages 22-28).  
• Unique features: lacks N-terminal myristoylation/palmitoylation motifs present in classical SFKs, explaining predominantly soluble cytoplasmic or nuclear localisation (unknownauthors2015effectsoffynrelated pages 35-39).  
• No full-length crystal structure; homology models and PTK6 crystal comparisons indicate canonical Src-like αC-helix and hydrophobic spine arrangement (thakur2016crystalstructureof pages 4-5).

## Regulation

Post-translational modifications  
– Autophosphorylation at Tyr387 increases catalytic activity (goel2016understandingthecellular pages 3-4).  
– C-terminal Tyr497 phosphorylation by CSK enforces SH2-mediated autoinhibition; Y497F mutation yields constitutive activity (goel2016understandingthecellular pages 2-3, unknownauthors2015effectsoffynrelated pages 1-5).  
– NEDD4 E3 ligase-mediated ubiquitination decreases FRK stability (goel2016understandingthecellular pages 1-2).

Conformational control  
Intramolecular SH3/SH2–linker interactions maintain a closed, inactive conformation analogous to Src family kinases (goel2016understandingthecellular pages 5-6).

## Function

Expression  
High in lung, liver, kidney, pancreas, mammary and intestinal epithelial cells (goel2016understandingthecellular pages 1-2).

Subcellular localisation  
Predominantly cytoplasmic with context-dependent nuclear pools governed by the SH2-embedded NLS (unknownauthors2015effectsoffynrelated pages 79-82).

Upstream regulators  
CSK (phosphorylates Tyr497) and NEDD4 (ubiquitinates FRK) (goel2016understandingthecellular pages 2-3, goel2016understandingthecellular pages 1-2).

Downstream substrates / pathways  
• PTEN phosphorylation stabilises PTEN, attenuating PI3K-AKT signalling (unknownauthors2015effectsoffynrelated pages 39-42).  
• Phosphorylation-dependent interaction with EGFR promotes receptor internalisation and suppresses EGFR signalling (goel2016understandingthecellular pages 6-8).  
• BRCA1 phosphorylation enhances BRCA1 stability within DNA-damage response pathways (unknownauthors2022theroleof pages 37-42).  
• FRK expression reduces STAT3, JNK and p38 MAPK phosphorylation, while elevating ERK1/2 activity in breast cancer cells (unknownauthors2015effectsoffynrelated pages 82-86).  
• SH3-mediated binding to pRb reinforces G1/S arrest (unknownauthors2015effectsoffynrelated pages 35-39).

Biological roles  
Negatively regulates proliferation, migration, invasion and anchorage-independent growth in breast cancer models; effects are amplified by constitutively active Y497F variant (unknownauthors2015effectsoffynrelated pages 65-73). Context-dependent oncogenic activity reported in hepatocellular carcinoma with activating FRK mutations (goel2016understandingthecellular pages 18-19).

## Inhibitors

• Broad-spectrum kinases staurosporine and dasatinib inhibit FRK activity in vitro (goel2016understandingthecellular pages 1-2, yang2010asilentmutation pages 3-4).  
• Additional screening compounds SU4984 and D-65495 show inhibitory activity toward FRK family kinases (goel2016understandingthecellular pages 18-19).

## Other Comments

• Loss of heterozygosity at 6q21-q22.3 encompassing FRK is found in ~48 % of breast tumours, melanomas and non-small cell lung cancers (goel2016understandingthecellular pages 1-2).  
• Oncogenic ETV6-FRK fusion proteins drive leukemogenesis in haematologic malignancies (goel2016understandingthecellular pages 18-19).  
• Activating point mutations in hepatocellular carcinoma render FRK constitutively active and correlate with elevated STAT3 signalling (goel2016understandingthecellular pages 1-2).  
• Elevated FRK mRNA expression associates with improved overall survival in breast cancer cohorts (goel2016understandingthecellular pages 16-18).

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