## Phylogeny

Tyrosine-protein kinase Fyn is a non-receptor tyrosine kinase classified within the Src family kinases (SFKs), a subgroup of the larger tyrosine kinase (TK) family within the human kinome (boubeva2011understandingtyrosinekinase pages 37-40, unknownauthors2021applicationofcomputational pages 14-17, yaronbarir2024theintrinsicsubstrate pages 1-2). According to the classification by Manning et al., 2002, Fyn is placed in the ‘SRC’ group of non-receptor tyrosine kinases (nRTKs) or cytoplasmic tyrosine kinases (CTKs) (boubeva2011understandingtyrosinekinase pages 37-40, yaronbarir2024theintrinsicsubstrate pages 2-2). Known orthologs include Mouse Fyn, Rat Fyn, Chicken Fyn (UniProt Q90Y79), and Zebrafish Fyn (UniProt Q7ZUM2) (yaronbarir2024theintrinsicsubstrate pages 4-4). The intrinsic substrate specificity of SFKs, including Fyn, is evolutionarily conserved, showing similarity between human kinases and their nematode orthologs (yaronbarir2024theintrinsicsubstrate pages 6-7).

## Reaction Catalyzed

The catalytic activity can be formally described by the chemical reaction: ATP + a [protein]-L-tyrosine = ADP + a [protein]-L-tyrosine phosphate (mannekumar2011virtualscreeningto pages 1-14, yaronbarir2024theintrinsicsubstrate pages 1-2).

## Cofactor Requirements

The catalytic activity of Fyn requires ATP as the phosphate donor and is dependent on the presence of divalent metal ions, typically Mg²⁺ or Mn²⁺, which facilitate ATP binding and phosphoryl transfer (yaronbarir2024theintrinsicsubstrate pages 5-5, yaronbarir2024theintrinsicsubstrate pages 1-2).

## Substrate Specificity

Fyn’s substrate specificity is determined by the recognition of consensus motifs containing amino acids flanking the target tyrosine, with high selectivity for residues in positions -1 to +3 (unknownauthors2021applicationofcomputational pages 111-114, yaronbarir2024theintrinsicsubstrate pages 3-3). As a non-receptor tyrosine kinase, Fyn is among the majority that favor a glutamate residue at the +1 position (yaronbarir2024theintrinsicsubstrate pages 3-4). The consensus motif generally shows a preference for aliphatic hydrophobic residues like isoleucine at positions -1 and +3, basophilic (positively charged) residues proximal to the phosphorylation site, and is enriched with proline residues near the target phosphotyrosine (yaronbarir2024theintrinsicsubstrate pages 3-3, yaronbarir2024theintrinsicsubstrate pages 5-5).

A prominent feature of Fyn is phosphopriming, where the kinase preferentially phosphorylates substrates that are already phosphorylated (yaronbarir2024theintrinsicsubstrate pages 3-4). Fyn favors substrates containing a phosphotyrosine (pY) at positions -1, +1, or +2 relative to the target tyrosine (yaronbarir2024theintrinsicsubstrate pages 16-17). Conversely, a phosphorylated residue at the +3 position can hinder phosphorylation through a ‘phospho-obstruction’ mechanism (yaronbarir2024theintrinsicsubstrate pages 6-7). Substrate recognition is also mediated by the SH2 domain, which preferentially binds phosphotyrosine-containing sequences with a pY-E-E-I motif (unknownauthors2021applicationofcomputational pages 17-21).

## Structure

Fyn kinase possesses the conserved modular structure of Src family kinases, organized from N- to C-terminus as: an SH4 domain, a unique domain, an SH3 domain, an SH2 domain, a catalytic kinase domain (SH1), and a C-terminal negative regulatory tail (unknownauthors2021applicationofcomputational pages 17-21). Crystallographic structures for the human FYN kinase domain are available in the Protein Data Bank under IDs 2DQ7, 2DQ8, and 2DQ9, and a computational model is available from AlphaFold for UniProt ID P06241 (unknownauthors2007exploringstructureand pages 72-75, mannekumar2011virtualscreeningto pages 1-14). - **SH4 Domain**: A ~15 amino acid N-terminal region containing a glycine that undergoes myristoylation for membrane anchorage (unknownauthors2021applicationofcomputational pages 17-21). - **Unique Domain**: A poorly conserved region of 40-70 amino acids that may function as a spacer (unknownauthors2021applicationofcomputational pages 17-21). - **SH3 Domain**: A ~50 residue domain with a β-barrel structure that recognizes and binds proline-rich sequences with a PxxP motif (unknownauthors2021applicationofcomputational pages 17-21). - **SH2 Domain**: A ~100 residue domain that binds phosphotyrosine-containing sequences, such as the pY-E-E-I motif (unknownauthors2021applicationofcomputational pages 17-21). - **Kinase Domain**: A bilobal structure with an N-terminal lobe (five β-sheets, αC-helix, P-loop) and a larger, predominantly α-helical C-terminal lobe (catalytic loop) (boubeva2011understandingtyrosinekinase pages 37-40, unknownauthors2007exploringstructureand pages 28-33). The ATP binding pocket is located in the cleft between the lobes (boubeva2011understandingtyrosinekinase pages 37-40). Key active site residues include LEU-17, GLY-18, LYS-39, and ASP-148 (mannekumar2011virtualscreeningto pages 1-14). - **Key Regulatory Features**: The kinase domain contains the flexible glycine-rich P-loop, the αC-helix, and the activation loop (A-loop) (boubeva2011understandingtyrosinekinase pages 40-45). The A-loop contains a conserved DFG motif and undergoes significant conformational changes between active (‘open’) and inactive (‘closed’) states (boubeva2011understandingtyrosinekinase pages 40-45). The active conformation is characterized by the DFG motif adopting a ‘DFG-in’ state and an inward-facing αC-helix forming a salt bridge between a conserved glutamate and lysine (boubeva2011understandingtyrosinekinase pages 40-45, unknownauthors2021applicationofcomputational pages 25-32).

## Regulation

Fyn activity is tightly controlled by post-translational modifications and conformational changes (boubeva2011understandingtyrosinekinase pages 40-45). The primary mechanism is dual tyrosine phosphorylation: - **Inhibitory Phosphorylation**: A tyrosine residue in the C-terminal tail (Tyr531 in Fyn) is phosphorylated by kinases such as C-terminal Src kinase (Csk) (unknownauthors2021applicationofcomputational pages 25-32, unknownauthors2021applicationofcomputational pages 17-21). This phosphotyrosine binds intramolecularly to Fyn’s own SH2 domain, while the SH3 domain binds a linker region, folding the kinase into a compact, autoinhibited conformation (boubeva2011understandingtyrosinekinase pages 40-45, unknownauthors2021applicationofcomputational pages 17-21). This inactive state displaces the αC-helix, disrupts a critical salt bridge involving Glu-310, and blocks the active site (unknownauthors2021applicationofcomputational pages 17-21). - **Activating Phosphorylation**: An activating tyrosine within the A-loop (analogous to Tyr416 in c-Src) undergoes autophosphorylation (unknownauthors2021applicationofcomputational pages 17-21). This modification stabilizes the A-loop in an open, active conformation that permits substrate access (boubeva2011understandingtyrosinekinase pages 40-45).

Activation of Fyn is initiated by the dephosphorylation of the inhibitory Tyr531 site or by competitive binding of external ligands to the SH2 or SH3 domains, which disrupts the autoinhibited structure (boubeva2011understandingtyrosinekinase pages 40-45). This allows for the subsequent autophosphorylation of the A-loop tyrosine, leading to full kinase activity (unknownauthors2021applicationofcomputational pages 17-21). The conformational state is also governed by the DFG motif at the N-terminus of the A-loop, which switches between a ‘DFG-in’ (active) and ‘DFG-out’ (inactive) state (boubeva2011understandingtyrosinekinase pages 40-45).

## Function

Fyn is ubiquitously expressed but found at particularly high levels in platelets, neurons, and osteoclasts (unknownauthors2021applicationofcomputational pages 21-25). It plays a pivotal role in diverse cellular processes, including cell growth, survival, differentiation, adhesion, and motility (mannekumar2011virtualscreeningto pages 1-14, unknownauthors2021applicationofcomputational pages 21-25). Fyn is a key mediator in signal transduction pathways, including integrin-mediated signaling, T-cell receptor signaling, Fc epsilon RI signaling, axon guidance, and immune responses (mannekumar2011virtualscreeningto pages 1-14).

Fyn associates with subcellular structures like focal adhesions and adherens junctions to regulate cytoskeletal dynamics (unknownauthors2021applicationofcomputational pages 21-25). Its expression is important for myelination in the central nervous system and brain development (mannekumar2011virtualscreeningto pages 1-14). Downstream signaling partners and substrates of Fyn include focal adhesion kinase (FAK), paxillin, SHP-2, PLCγ2, SHC, WAS, MAP2, and MAPT (mannekumar2011virtualscreeningto pages 1-14, yaronbarir2024theintrinsicsubstrate pages 5-5). It also interacts with proteins such as ELMO1 and CRKL and influences pathways involving the MET and FLT3 receptors (yaronbarir2024theintrinsicsubstrate pages 5-5).

## Inhibitors

Several compounds are known to inhibit Fyn kinase. These include the broad-spectrum kinase inhibitors Staurosporine and Dasatinib, as well as Rosmarinic acid (mannekumar2011virtualscreeningto pages 1-14). Other identified inhibitors include Si308 and its pyrazolo[3,4-d]pyrimidine derivatives, and the multi-SFK inhibitor masitinib (unknownauthors2021applicationofcomputational pages 111-114, unknownauthors2021applicationofcomputational pages 21-25). Bosutinib is also a relevant SFK inhibitor for Fyn (yaronbarir2024theintrinsicsubstrate pages 16-16). Virtual screening studies have identified Nordihydroguaiaretic acid (NDGA) and Phyllodulcin as potential inhibitors with high binding affinity to Fyn’s active site (mannekumar2011virtualscreeningto pages 14-23).

## Other Comments

Dysregulation of Fyn is associated with multiple human diseases (mannekumar2011virtualscreeningto pages 1-14). Hyperactivation or overexpression is implicated in numerous cancers, including neuroblastoma, metastatic melanoma, lung squamous cell carcinoma, breast cancer, glioblastoma, and lymphomas (mannekumar2011virtualscreeningto pages 1-14, unknownauthors2021applicationofcomputational pages 21-25). Fyn is also linked to neurological conditions such as epilepsy and Alzheimer’s disease, where it may modulate tau phosphorylation and amyloid-beta toxicity (mannekumar2011virtualscreeningto pages 1-14, yaronbarir2024theintrinsicsubstrate pages 16-16).

Specific mutations in Fyn have been identified in disease contexts: - **V137L**: A mutation replacing valine with leucine at position 137 causes Fyn overexpression and is associated with lung squamous cell carcinoma (mannekumar2011virtualscreeningto pages 1-14). - **Y531H**: A mutation substituting histidine for the inhibitory tyrosine at position 531 is an activating mutation found in peripheral T-cell lymphoma (unknownauthors2021applicationofcomputational pages 25-32).

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