## Phylogeny

Human Lyn (UniProt P07948) belongs to the Tyrosine Kinase (TK) group, Src-family branch, Lyn/Hck sub-subfamily as defined in the kinome census (ingley2012functionsofthe pages 1-2). Orthologs with high sequence conservation are documented in Mus musculus, Rattus norvegicus, Danio rerio and Gallus gallus, and the Drosophila paralogue Src42A represents the invertebrate counterpart (berndt2019crystalstructureof pages 8-10, ingley2012functionsofthe pages 1-2). Within the Src family, Lyn clusters most closely with Hck, Lck and Blk, reflecting a recent duplication that generated the Lyn-related sub-branch (unknownauthors2018lynregulatesdrug pages 17-22).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (unknownauthors2018lynregulatesdrug pages 17-22).

## Cofactor Requirements

Catalytic turnover requires a divalent metal ion; either Mg²⁺ or Mn²⁺ can occupy the nucleotide-binding site and coordinate the β- and γ-phosphates of ATP (berndt2019crystalstructureof pages 8-10, ingley2012functionsofthe pages 1-2).

## Substrate Specificity

A recent high-throughput phosphoproteomics survey refined Lyn’s intrinsic consensus around the target tyrosine, favouring acidic or small residues at the +1 position and hydrophobic residues at +3 (berndt2019crystalstructureof pages 8-10). In immune signalling contexts Lyn phosphorylates canonical ITAM motifs (YxxL/Ix₆–₁₂YxxL/I) and ITIM motifs (S/I/V/LxYxxL/V) present in immunoreceptors (weerawarna2023lynkinasestructure pages 1-3).

## Structure

Domain organisation: SH4 (Met-Gly-Cys myristoylation/palmitoylation motif) – Unique – SH3 – SH2 – Kinase (SH1) – C-terminal regulatory tail (ingley2012functionsofthe pages 1-2).  
• SH3 domain: five-stranded β-barrel; ligand pocket formed by Tyr74, Trp99 and Pro114; crystal structure solved at 1.3 Å (PDB 1W1F) (berndt2019crystalstructureof pages 4-6).  
• SH2 domain: canonical α/β fold; phosphorylation of EF-loop Tyr194 remodels the phosphotyrosine pocket and modulates ligand preference; structure deposited as PDB 4TZI (jin2015tyrosinephosphorylationof pages 10-14, jin2015tyrosinephosphorylationof pages 22-25).  
• Kinase domain: bilobal Src-like fold with Lys275-Glu290 catalytic salt bridge, HRD motif His371-Arg372-Asp373, and DFG motif Asp385-Phe386-Gly387; autophosphorylation site Tyr397 resides in the activation loop; active DFG-in/αC-in structures include PDB 3ERP and 4RJ3 (weerawarna2023lynkinasestructure pages 4-7, berndt2019crystalstructureof pages 7-8).  
• C-terminal tail carries inhibitory Tyr508 that docks into the SH2 domain to stabilise the closed conformation (ingley2012functionsofthe pages 1-2).  
No full-length Lyn structure has been solved; the autoinhibited topology is inferred from Src-family templates showing simultaneous SH3-linker and SH2-tail contacts (berndt2019crystalstructureof pages 4-6).

## Regulation

Post-translational modifications  
– Tyr508: phosphorylated by Csk or Chk to generate an SH2-binding site that suppresses kinase activity (ingley2012functionsofthe pages 1-2, unknownauthors2018lynregulatesdrug pages 17-22).  
– Tyr397: autophosphorylated following Tyr508 dephosphorylation; required for full catalytic competence (ingley2012functionsofthe pages 1-2, kinoshita2008proteinpurificationand pages 5-6).  
– Tyr194 (SH2): phosphorylated by EphA4, PDGFR or Syk, decreasing affinity for canonical pYEEI ligands and redirecting binding specificity (jin2015tyrosinephosphorylationof pages 22-25).  
– Tyr32 (unique domain): isoform-specific site phosphorylated downstream of EGFR, with incompletely defined functional consequences (weerawarna2023lynkinasestructure pages 3-4).  
– Ser13 (SH4): phosphorylated by CK1γ at the Golgi; modification attenuates electrostatic membrane interactions during trafficking (kinoshitakikuta2020proteinnmyristoylationdependentphosphorylationof pages 10-10).

Dephosphorylation  
CD45 and SHP-2 remove pTyr508 to initiate activation, whereas SHP-1 and SHP-2 dephosphorylate pTyr397 to terminate signalling (ingley2012functionsofthe pages 1-2).

Ubiquitination  
The E3 ligase c-Cbl interacts via the Lyn SH3 domain and polyubiquitinates active Lyn, targeting it for proteasomal degradation (weerawarna2023lynkinasestructure pages 10-12, sun2021theroleof pages 6-6).

Conformational control  
Intramolecular SH3-linker and SH2-pTyr508 engagements lock the kinase in an αC-out inactive state; disengagement or mutation of either interface yields constitutive activation (berndt2019crystalstructureof pages 4-6).

## Function

Expression  
Highly expressed in B cells, mast cells, macrophages, platelets and brain neurons/microglia; absent in resting T lymphocytes (ingley2012functionsofthe pages 1-2, weerawarna2023lynkinasestructure pages 10-12).

Upstream receptors  
B-cell receptor components CD79A/B, CD19, CD22, FcεRI, FcγRI/II, TLR2, TLR4 and various growth-factor receptors recruit and activate Lyn (ingley2012functionsofthe pages 1-2, berndt2019crystalstructureof pages 6-7).

Downstream partners and substrates  
Key signalling nodes include SYK, BTK, PLCγ2 and PI3K; additional substrates comprise β-catenin, N-myristoyl-transferase-1, STAT3, Na⁺/K⁺-ATPase α3 and NMDA receptor subunits (berndt2019crystalstructureof pages 1-2, weerawarna2023lynkinasestructure pages 10-12).

Pathways  
Lyn phosphorylates ITAMs and ITIMs to fine-tune immune-receptor signalling, drives PI3K–NF-κB activation downstream of TLR2, regulates platelet activation and integrin outside-in signalling, and modulates neuronal responses to amyloid-β in Alzheimer’s disease models (berndt2019crystalstructureof pages 6-7, weerawarna2023lynkinasestructure pages 10-12).

## Inhibitors

Clinically deployed multi-kinase inhibitors with nanomolar Lyn potency include Dasatinib, Bosutinib, Ponatinib, Nintedanib, Bafetinib and the investigational agent Saracatinib; a benzimidazole scaffold Lyn-INH-59 provides greater selectivity in experimental settings (berndt2019crystalstructureof pages 1-2, berndt2019crystalstructureof pages 7-8, berndt2019crystalstructureof pages 8-10).

## Other Comments

Over-expression or gain-of-function activation of Lyn is documented in acute myeloid leukaemia, breast, colorectal, renal, ovarian and lung cancers, where it correlates with poor prognosis (berndt2019crystalstructureof pages 1-2). Germline missense and nonsense mutations at Tyr508 (p.Tyr508His, p.Tyr508Phe, p.Tyr508\*) cause early-onset systemic autoinflammatory disease through constitutive kinase activation (unknownauthors2022denovogain‐of‐function pages 3-3). Somatic cancer-associated mutations across the SH3 domain (e.g., D81N, W99L, E98K, V118M) destabilise the autoinhibited fold and elevate kinase activity (berndt2019crystalstructureof pages 4-6). Lyn-null mice develop lupus-like autoimmunity, underscoring its role in immune self-tolerance (berndt2019crystalstructureof pages 8-10).

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