## Phylogeny

EphB2 belongs to the tyrosine kinase (TK) group, receptor tyrosine kinase (RTK) family, Eph receptor sub-family, EphB subclass (Overman et al., 2013, pp. 1–2; Berrou et al., 2018, pp. 1–5).  
Within the EphB branch the catalytic domains are highly conserved (~88 % identity); EphB2 shares 83 % identity with EphB4, indicating recent divergence (Overman et al., 2013, pp. 11–14).  
Orthologous kinase domains are retained across vertebrates, reflecting strong evolutionary constraint (Berrou et al., 2018, pp. 5–9).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (Unknown authors, 2014, pp. 5–9; Berrou et al., 2018, pp. 5–9).

## Cofactor Requirements

Catalytic activity requires divalent cations; assays are performed with Mg²⁺ and ATP (Unknown authors, 2023, pp. 94–100).

## Substrate Specificity

A defined linear phosphorylation motif has not been established; substrate preferences remain undetermined (Overman et al., 2013, pp. 9–10).

## Structure

Domain order: ligand-binding domain → cysteine-rich region → two fibronectin type III domains → single transmembrane helix → juxtamembrane segment (JMS) → kinase domain (KD) → sterile-alpha motif → C-terminal PDZ-binding motif (Unknown authors, 2014, pp. 5–9).  
Autoinhibition: the JMS contacts αC and β4 of the KD, disorganising the activation segment; ephrin-induced receptor clustering relieves this brake (Unknown authors, 2014, pp. 5–9).  
Catalytic core: Lys721 (β3) pairs with Glu739 (αC) for ATP positioning; Asp746 functions as catalytic base; Arg745 supports nucleotide binding—mutation R745C disrupts this triad (Berrou et al., 2018, pp. 5–9).  
Regulatory tyrosines: Y594/Y604 (alternative numbering Y605/Y611) in the JMS are the primary activation switch; their phosphorylation both orders the activation loop and generates SH2 docking sites (Berrou et al., 2018, pp. 16–20; Zisch et al., 2000, pp. 1–2).  
Structural data: KD crystal structure solved with ADP (PDB 2HEN) confirms a canonical bilobal fold (Unknown authors, 2023, pp. 94–100).  
Selectivity feature: Ser706 in the hinge (EphB4 numbering) is unique within EphB kinases and can be exploited for isozyme-selective inhibition (Overman et al., 2014, pp. 7–9).

## Regulation

• Ligand-driven clustering triggers trans-autophosphorylation of Y594/Y604, releasing JMS autoinhibition and activating the kinase (Unknown authors, 2014, pp. 5–9; Berrou et al., 2018, pp. 16–20).  
• Phosphorylated Y594/Y604 recruit SH2-domain proteins (Src, Fyn, RasGAP, Nck, Crk) to propagate signalling (Zisch et al., 2000, pp. 6–8).  
• Y605/Y611→Phe abolishes kinase activity; Glu substitution preserves catalysis but blocks SH2 binding, uncoupling activation from adaptor recruitment (Zisch et al., 2000, pp. 1–2).  
• Missense variant p.R745C in the KD eliminates autophosphorylation, reduces Src activation and impairs downstream signalling in platelets (Berrou et al., 2018, pp. 16–20).  
• Recombinant kinase expression requires co-expression of a phosphatase to keep the KD unphosphorylated (Overman et al., 2013, pp. 7–8).

## Function

Platelets: EphB2 enhances GPVI and G-protein-coupled receptor pathways, promoting αIIbβ3 activation, dense-granule secretion, aggregation and thrombus stability (Berrou et al., 2018, pp. 1–5).  
Neural development: controls commissural axon guidance, inner-ear efferent targeting, retinal ganglion routing, dendritic spine maturation and excitatory synapse formation (Lisabeth et al., 2013, pp. 1–2).  
Additional roles: vascular development, tissue boundary formation, bone homeostasis and pancreatic β-cell communication (Berrou et al., 2018, pp. 16–20).  
Expression: high in platelets and broadly present in neural and developmental tissues (Berrou et al., 2018, pp. 1–5; Lisabeth et al., 2013, pp. 1–2).  
Signalling partners: upstream ephrin-B ligands; downstream effectors include Src family kinases (Src, Lyn), Syk, PLCγ2, PI3K/Akt and cytoskeletal regulators RasGAP and Nck (Berrou et al., 2018, pp. 16–20; Zisch et al., 2000, pp. 6–8).

## Inhibitors

ATP-competitive agents: CMPD1 is potent against EphB2; potency drops for EphB3 owing to hinge residue variation (Overman et al., 2013, pp. 7–8).  
Broad-spectrum TKIs such as dasatinib and NVP-BHG712 act across the Eph family with limited isoform selectivity (Overman et al., 2013, pp. 9–10).  
Structure–activity work highlights conserved Gly699 (EphB4 numbering) as critical for inhibitor binding, complicating isoform-specific design (Overman et al., 2013, pp. 7–8).

## Other Comments

• Homozygous p.R745C causes a recessive platelet function defect and severe bleeding (Berrou et al., 2018, pp. 1–5; pp. 5–9).  
• Loss-of-function mutations and reduced activity are reported in prostate and colorectal cancers, supporting a tumour-suppressor role (Lisabeth et al., 2013, pp. 12–13; Overman et al., 2013, pp. 1–2).  
• Platelets lack compensatory Eph receptors, explaining the isolated haemostatic phenotype in EPHB2-deficient individuals (Berrou et al., 2018, pp. 16–20).

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