## Phylogeny

EPHA6 belongs to the Receptor Tyrosine Kinase (RTK) group, Eph family, EphA subfamily in the human kinome (hunter2015theeukaryoticprotein pages 3-6).  
The human gene is an ortholog of rodent EphA6; additional orthologs are annotated in zebrafish, chicken and frog, with conserved substrate specificity across these vertebrates (robinson2000theproteintyrosine pages 6-8, yaronbarir2024theintrinsicsubstrate pages 1-2).  
Phylogenetic analyses separate catalytically competent EphA kinases, such as EPHA6, from the catalytically inactive EphA10 and from the distinct pseudokinase EphB6 lineage (liang2019ephreceptorsignalling pages 1-2).

## Reaction Catalyzed

ATP + protein L-tyrosine → ADP + protein L-tyrosine phosphate (liang2019ephreceptorsignalling pages 1-2).

## Cofactor Requirements

Catalysis by Eph receptor kinase domains requires a divalent cation, typically Mg²⁺ or Mn²⁺, for ATP coordination (strozen2021theephb6receptor pages 7-8).

## Substrate Specificity

A positional-scanning peptide array defined an EphA-subclass consensus phosphotyrosine motif recognised by EPHA6; the preferred residue pattern flanking the target tyrosine is conserved in mouse, zebrafish, chicken and frog orthologs (yaronbarir2024theintrinsicsubstrate pages 1-2).

## Structure

EPHA6 contains an N-terminal ligand-binding domain, a cysteine-rich region, two fibronectin type-III repeats, a single transmembrane helix, an intracellular juxtamembrane segment, a bilobal tyrosine kinase domain, a sterile-alpha motif (SAM) domain and a C-terminal PDZ-binding motif (liang2019ephreceptorsignalling pages 1-2).  
Crystal structures of related EphA kinases (e.g., EphA2, PDB 3HEI/2P2H) reveal the canonical αC-helix, activation loop and hydrophobic spine that are sequence-conserved in EPHA6 (wei2014structuresofan pages 8-9).  
The human EPHA6 transcript contains a cryptic splice within kinase sub-domain VIII and unused exons for sub-domains IX–XI, producing a truncated kinase region and divergence in several catalytic signature residues (robinson2000theproteintyrosine pages 6-8).  
A V/I-E/Q-V PDZ-binding motif at the extreme C-terminus mediates interaction with PDZ domains such as AF6 (hock1998pdzdomainmediatedinteractionof pages 4-5).

## Regulation

Autoinhibitory contacts between juxtamembrane tyrosines JX1 and JX2 and the αC-helix are relieved by their phosphorylation, enabling kinase activation in catalytically competent EphA receptors (liang2019ephreceptorsignalling pages 4-6).  
SAM-domain phosphorylation modulates receptor oligomerization and adaptor recruitment (liang2019ephreceptorsignalling pages 4-6).  
The C-terminal PDZ-binding motif associates with AF6; this interaction in cells depends on receptor autophosphorylation (hock1998pdzdomainmediatedinteractionof pages 4-5).  
No additional post-translational modifications or allosteric regulators specific to EPHA6 were reported in the provided sources.

## Function

EPHA6 transcripts are predominant in neural tissues and are detected in prostate epithelium and vascular endothelium (hafner2004differentialgeneexpression pages 10-10).  
The receptor engages GPI-anchored ephrin-A ligands on adjacent cells, initiating forward signalling in the EPHA6-bearing cell and reverse signalling in the ephrin-expressing cell (liang2019ephreceptorsignalling pages 1-2).  
Family-wide downstream pathways include Rho-GTPase-mediated cytoskeletal remodelling and modulation of ERK and Akt cascades (liang2019ephreceptorsignalling pages 1-2).  
The PDZ adaptor AF6 interacts with the EPHA6 C-terminus and can itself be phosphorylated by kinase-active Eph receptors, linking EPHA6 to junctional signalling networks (hock1998pdzdomainmediatedinteractionof pages 4-5).  
EPHA6 expression correlates with enhanced angiogenesis and metastatic propensity in prostate cancer models (buckens2020theroleof pages 31-34).

## Other Comments

EPHA6 over-expression associates with prostate cancer progression and metastasis (buckens2020theroleof pages 31-34).  
The cryptic splice in the human kinase domain leaves the in-vivo catalytic competence of EPHA6 unresolved (robinson2000theproteintyrosine pages 6-8).

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