## Phylogeny

EPHA1 is a receptor tyrosine kinase (RTK) belonging to the Eph (erythropoietin-producing hepatocellular carcinoma) receptor family, the largest RTK subfamily in mammals (unknownauthors2019characterisationofepha1 pages 52-56, barquilla2015ephreceptorsand pages 1-2, surawska2004theroleof pages 1-2). As classified by Manning et al., it is a member of the tyrosine kinase group (matsumoto2025missensemutationsof pages 1-2, matsumoto2025missensemutationsof pages 15-16, bocharov2008spatialstructureand pages 1-2). Within the Eph family, it is assigned to the A-subclass based on sequence homology and preferential binding to ephrin-A ligands (unknownauthors2019characterisationofepha1 pages 52-56, surawska2004theroleof pages 1-2). The murine EphA1 gene shows synteny with its human homologue (coulthard2001characterizationofthe pages 1-3).

## Reaction Catalyzed

ATP + a [protein]-L-tyrosine = ADP + a [protein]-L-tyrosine phosphate (matsumoto2025missensemutationsof pages 1-2, matsumoto2025missensemutationsof pages 16-16, matsumoto2025missensemutationsof pages 15-16, unknownauthors2019characterisationofepha1 pages 102-107).

## Cofactor Requirements

Catalytic activity requires Mg2+ as a cofactor (matsumoto2025missensemutationsof pages 1-2, barquilla2015ephreceptorsand pages 1-2, masuda2008fibronectintypei pages 9-9, bocharov2008spatialstructureand pages 1-2).

## Substrate Specificity

Based on positional scanning peptide array (PSPA) analysis, EPHA1 is classified within Specificity Group 3, the Ephrin receptors group (yaronbarir2024theintrinsicsubstrate pages 2-2). The consensus motif for this group shows a preference for proline (P) and acidic residues at positions P-1 to P-3, with an enrichment of glycine (G) residues at positions P+1 to P+4 relative to the phosphorylated tyrosine (yaronbarir2024theintrinsicsubstrate pages 16-16). EPHA1 also shows phosphopriming preferences, with moderate selectivity for phosphotyrosine (pY) residues at substrate positions flanking the phosphorylation site, particularly at P+1 or P+2 (yaronbarir2024theintrinsicsubstrate pages 16-17).

## Structure

EPHA1 is a single-pass transmembrane protein with a multi-domain architecture consisting of an extracellular region, a transmembrane α-helix, and an intracellular region (unknownauthors2019characterisationofepha1 pages 52-56, barquilla2015ephreceptorsand pages 1-2). The extracellular region (aa 26-547) contains an N-terminal ligand-binding domain with a complex jellyroll structure, a cysteine-rich region, an EGF-like domain, and two fibronectin type-III (FNIII) repeats (unknownauthors2019characterisationofepha1 pages 102-107, bocharov2008spatialstructureand pages 1-2, coulthard2001characterizationofthe pages 5-7). The transmembrane domain dimerizes into a right-handed parallel alpha-helical structure via a glycine zipper motif, exhibiting pH-dependent conformational diversity (bocharov2008spatialstructureand pages 1-2). The intracellular region contains a regulatory juxtamembrane segment, a dual-lobe kinase domain, a sterile alpha motif (SAM) domain, and a kinase-SAM linker (matsumoto2025missensemutationsof pages 1-2, unknownauthors2019characterisationofepha1 pages 52-56). While specific 3D structural data for EPHA1 is limited, insights are drawn from the structurally characterized kinase domain of its close homolog EphA2 (e.g., PDB IDs 3FL7, 3MXT), and a high-confidence predicted structure for full-length human EPHA1 is provided by AlphaFold (unknownauthors2019characterisationofepha1 pages 52-56). Key regulatory features inferred from the EphA2 structure include the C-helix, which rotates to facilitate ATP binding in the active state, and the hydrophobic spine, a set of conserved residues that forms a continuous alignment to stabilize the active conformation and is disrupted in the inactive state (unknownauthors2019characterisationofepha1 pages 52-56). Unlike many Eph receptors, EPHA1 lacks a PDZ-binding motif, though some sources report its presence (unknownauthors2019characterisationofepha1 pages 52-56, barquilla2015ephreceptorsand pages 1-2, surawska2004theroleof pages 2-3).

## Regulation

EPHA1 activity is regulated by ligand binding, which induces receptor clustering and dimerization, leading to trans-autophosphorylation on specific tyrosine residues within the juxtamembrane region and the kinase domain’s activation loop (barquilla2015ephreceptorsand pages 1-2, surawska2004theroleof pages 2-3). In addition to tyrosine phosphorylation, EPHA1 is phosphorylated on serine residues S906, S908, and S910 within the kinase-SAM linker region (matsumoto2025missensemutationsof pages 1-2). Receptor turnover and signal termination are modulated by ubiquitination, internalization via clathrin-mediated endocytosis, and proteolytic cleavage (unknownauthors2019characterisationofepha1 pages 102-107, unknownauthors2019characterisationofepha1 pages 59-63). Cleavage is performed by proteases including matrix metalloproteinases (MMPs), ADAMs (ADAM10, ADAM12), and γ-secretase (unknownauthors2019characterisationofepha1 pages 102-107, unknownauthors2019characterisationofepha1 pages 59-63). EPHA1 expression is also regulated epigenetically via methylation of its CpG island (herath2010theroleof pages 5-6, pasquale2010ephreceptorsand pages 13-13).

## Function

EPHA1 is expressed in differentiated epithelial tissues (e.g., skin, colon, liver, kidney, thymus), immune cells, and the brain (coulthard2001characterizationofthe pages 1-3, matsumoto2025missensemutationsof pages 1-2, herath2010theroleof pages 5-6). It functions as a receptor for membrane-bound ephrin-A ligands, with ephrin-A1 being its primary, high-affinity ligand, to mediate contact-dependent bidirectional signaling (unknownauthors2019characterisationofepha1 pages 102-107, barquilla2015ephreceptorsand pages 1-2). Forward signaling through EPHA1 regulates cell adhesion, repulsion, migration, proliferation, and angiogenesis (barquilla2015ephreceptorsand pages 1-2, unknownauthors2019characterisationofepha1 pages 59-63). Downstream signaling pathways include the PI3K/mTOR pathway, which is involved in tumor angiogenesis, and pathways that regulate Rho-GTPase activity (unknownauthors2019characterisationofepha1 pages 59-63, matsumoto2025missensemutationsof pages 16-16). Other pathways linked to Eph receptors include Jak/Stat (surawska2004theroleof pages 2-3). A fibronectin type I repeat acts as a non-activating ligand, inhibiting ATF3-dependent angiogenesis (masuda2008fibronectintypei pages 9-9).

## Other Comments

Dysregulation of EPHA1 is associated with cancer and Alzheimer’s disease (AD) (matsumoto2025missensemutationsof pages 1-2, surawska2004theroleof pages 1-2). In colorectal cancer, EPHA1 expression is often lost in advanced disease stages via epigenetic silencing, and this downregulation correlates with poor survival outcomes (pasquale2010ephreceptorsand pages 13-13, herath2010theroleof pages 5-6). Several missense mutations in EPHA1 are associated with late-onset sporadic AD (unknownauthors2019characterisationofepha1 pages 52-56, matsumoto2025missensemutationsof pages 15-16). AD-associated mutations such as P460L (FN2 domain), R492Q (FN2 domain), R791H (kinase domain), and R926C (SAM domain) disrupt EPHA1 tyrosine and serine phosphorylation, impair kinase activity, alter cell surface localization, and induce proteasomal degradation, thereby altering signaling relevant to neuroinflammation and blood-brain barrier function (matsumoto2025missensemutationsof pages 1-2, matsumoto2025missensemutationsof pages 16-16).

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