Phylogeny  
• Kinome lineage: Protein Tyrosine Kinase group → Eph family → EphA subclass → EPHA7 (choi2009discoveryandstructural pages 1-2, toracchio2024epha2incancer pages 14-16).  
• Orthologs: Mus musculus Epha7 (gale1996ephreceptorsand pages 11-11), Gallus gallus Epha7 in limb buds (toracchio2024epha2incancer pages 14-16), Danio rerio epha7a/epha7b (buckens2020theroleof pages 31-34), Xenopus Epha7 (gale1996ephreceptorsand pages 11-11), ancestral Drosophila Eph (buckens2020theroleof pages 31-34).  
• Closest paralogs: EPHA6 and EPHA4 within the EphA branch (toracchio2024epha2incancer pages 14-16).

Reaction Catalyzed  
ATP + protein-L-tyrosine → ADP + protein-L-tyrosine-phosphate (chakraborty2021crystalstructureof pages 5-6).

Cofactor Requirements  
Mg²⁺ is required; coordinated by Asp776 of the DFG motif (choi2009discoveryandstructural pages 4-5).

Substrate Specificity  
• Eph kinases preferentially target tyrosines flanked by acidic residues; consensus motif D/E-x-pY-x-D/E (toracchio2024epha2incancer pages 14-16, gale1996ephreceptorsand pages 11-11).  
• No EPHA7-specific divergence from this pattern has been reported (toracchio2024epha2incancer pages 14-16).

Structure  
• Domain order: ligand-binding → cysteine-rich → 2 × fibronectin-III → transmembrane → juxtamembrane → kinase → SAM → PDZ-binding motif (toracchio2024epha2incancer pages 1-2, gale1996ephreceptorsand pages 11-11).  
• 2.0 Å crystal structure with inhibitor 9 shows inactive DFG-out conformation and enlarged hydrophobic pocket (choi2009discoveryandstructural pages 2-4).  
• Catalytic triad: Lys665–Glu682 salt bridge and Asp776 in the DFG motif (chakraborty2021crystalstructureof pages 5-6, choi2009discoveryandstructural pages 4-5).  
• Activation loop Tyr791 undergoes autophosphorylation for full activity (li2017liganddependentepha7signaling pages 8-9).  
• Gatekeeper Ile707 removes a hinge H-bond accepted by Thr in other EphA kinases, reducing affinity for some type II inhibitors (choi2009discoveryandstructural pages 4-5).  
• Pathogenic mutants Gly656Arg/Glu and Asp751His distort the N-lobe and weaken ATP binding (chakraborty2021crystalstructureof pages 5-6).

Regulation  
• Tyr791 autophosphorylation activates kinase and tumour-suppressive signalling (li2017liganddependentepha7signaling pages 8-9).  
• Juxtamembrane tyrosine phosphorylation relieves autoinhibition after ephrin binding (gale1996ephreceptorsand pages 11-11).  
• Cbl-mediated ubiquitination targets receptor for degradation (toracchio2024epha2incancer pages 14-16).  
• ADAM10-dependent ectodomain shedding reduces surface receptor levels (toracchio2024epha2incancer pages 14-16).  
• Additional serine/threonine phosphorylation events modulate turnover and pathway choice (gale1996ephreceptorsand pages 11-11).  
• Ligand-induced oligomerisation drives DFG-in ↔ DFG-out transitions captured structurally (choi2009discoveryandstructural pages 2-4).

Function  
• Expression: enriched in developing and adult CNS (gale1996ephreceptorsand pages 11-11, leonard2020epha7isoformsdifferentially pages 21-22); present in prostate and other epithelia (guan2009aberrantmethylationof pages 7-7).  
• Ligand binding: high-affinity interaction with ephrin-A5; initiates bidirectional signalling (gale1996ephreceptorsand pages 11-11).  
• Downstream effects: inhibits PI3K/Akt (reduced Akt-Thr308/Ser473 phosphorylation) and shifts Bax/Bcl-2 toward apoptosis (li2017liganddependentepha7signaling pages 8-9); activates ERK and Rho GTPases via SHC1 and VAV2 adaptors (buckens2020theroleof pages 31-34).  
• Interactors: SHC1, VAV2 (buckens2020theroleof pages 31-34); TNFR1 (li2017liganddependentepha7signaling pages 8-9); focal adhesion kinase in integrin complexes (wilkinson2001multiplerolesof pages 10-10).  
• Biological roles: axon repulsion in corticothalamic and retinocollicular mapping (gale1996ephreceptorsand pages 11-11); regulation of cortical dendrite growth by kinase-active versus truncated isoforms (leonard2020epha7isoformsdifferentially pages 21-22); caspase-3-dependent apoptosis in neural progenitors and prostate cancer cells (li2017liganddependentepha7signaling pages 8-9).

Inhibitors  
• Type II inhibitors 6 and 9 bind the DFG-out pocket; compound 9 shows nanomolar inhibition of EPHA7 despite reduced affinity from Ile707 gatekeeper (choi2009discoveryandstructural pages 2-4, choi2009discoveryandstructural pages 4-5).  
• Broad-spectrum RTK inhibitors nilotinib and dasatinib exhibit measurable activity in profiling assays (choi2009discoveryandstructural pages 1-2).

Other Comments  
• Promoter hypermethylation associates with aggressive prostate cancer (guan2009aberrantmethylationof pages 7-7).  
• Haploinsufficiency or focal deletions cause neurodevelopmental disorders with microcephaly and intellectual disability (levy2021epha7haploinsufficiencyis pages 1-2).  
• Somatic mutations Gly656Arg, Gly656Glu and Asp751His reduce catalytic efficiency and are linked to cancer (chakraborty2021crystalstructureof pages 5-6).  
• EPHA7 deregulation via methylation or mutation is reported in colorectal, lung, melanoma and osteosarcoma (chakraborty2021crystalstructureof pages 6-6, toracchio2024epha2incancer pages 14-16).

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