## Phylogeny

DDR1 is classified within the Tyrosine Kinase (TK) group, Discoidin Domain Receptor (DDR) family of the human kinome (kothiwale2015discoidindomainreceptor pages 1-2).  
The catalytic domain shares 68 % sequence identity with DDR2 and aligns with ABL1 at 3.6 Å Cα RMSD, indicating evolutionary conservation of the bilobal kinase fold (canning2014structuralmechanismsdetermining pages 3-5, canning2014structuralmechanismsdetermining pages 5-6).  
Orthologs are documented across vertebrates, with mouse Ddr1 experimentally characterised and additional DDR1 genes reported in other vertebrate lineages (mariadoss2023exploringthecellular pages 16-18, mariadoss2023exploringthecellular pages 4-5).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (kothiwale2015discoidindomainreceptor pages 1-2).

## Cofactor Requirements

Catalytic activity requires divalent cations; in vitro kinase assays employ Mg²⁺ to support phosphoryl transfer (hanson2019whatmakesa pages 13-15).

## Substrate Specificity

• Autophosphorylation targets a YxYxY motif in the activation loop (Tyr792, Tyr796, Tyr797) and Tyr513 in the juxtamembrane region (kothiwale2015discoidindomainreceptor pages 1-2, juskaite2017collageninducesactivation pages 24-25).  
• Kinase-substrate docking studies identified Axltide (KKSRGDYMTMQIG) as an efficient exogenous substrate, indicating preference for basic residues −3/−2 to the phospho-acceptor tyrosine and a methionine at +2 (hanson2019whatmakesa pages 13-15).  
• Phosphotyrosine proteomics shows recruitment of SH2/PTB adaptors (SHC1, NCK2, RasGAP, SHIP1/2, PI3K p85) to multiple intracellular pTyr motifs, underscoring broad recognition of pY-containing sequences for signalling complex assembly (lemeer2012phosphotyrosinemediatedprotein pages 1-2).

## Structure

Domain organisation: DS domain – DS-like domain – single transmembrane helix – long cytoplasmic juxtamembrane segment – kinase domain (carafoli2013collagenrecognitionand pages 2-3, juskaite2017collageninducesactivation pages 1-2).  
Extracellular region:  
‐ DS domain adopts an eight-stranded β-barrel that recognises the GVMGFO motif in triple-helical collagen (carafoli2013collagenrecognitionand pages 3-4).  
‐ DS-like domain forms a jelly-roll fold with two N-glycans and a Ca²⁺ site, contributing to ectodomain rigidity (carafoli2012structureofthe pages 2-3).  
Kinase domain (PDB 3ZOS, 4BKJ):  
‐ Canonical bilobal fold with a β-hairpin P-loop, intact αC helix (Glu672) and HRD motif (His764-Arg765-Asp766) (canning2014structuralmechanismsdetermining pages 3-5, kothiwale2015discoidindomainreceptor pages 2-4).  
‐ DFG motif (Asp784-Phe785-Gly786) adopts an inactive Asp-out orientation in solved complexes; the Asp671–Arg752 ion pair locks this conformation and shelters the allosteric pocket (hanson2019whatmakesa pages 3-5).  
‐ A Lys655–Glu672 salt bridge anchors ATP; hydrophobic spine residues (Met676, Leu687, His764, Phe785) align upon activation (kothiwale2015discoidindomainreceptor pages 2-4).  
‐ The P-loop β-hairpin (residues 618-624) replaces the cage-like ABL1 loop, modulating inhibitor accommodation (canning2014structuralmechanismsdetermining pages 1-3).

## Regulation

Post-translational modifications  
‐ Autophosphorylation at Tyr513, Tyr792, Tyr796, Tyr797 following collagen binding promotes full catalytic activation and creates docking sites for SH2/PTB adaptors (juskaite2017collageninducesactivation pages 24-25, lemeer2012phosphotyrosinemediatedprotein pages 1-2).  
‐ Fifteen intracellular tyrosines collectively orchestrate recruitment of SHC1, NCK2, PI3K p85, RasGAP, SHIP1/2 and STAT proteins (lemeer2012phosphotyrosinemediatedprotein pages 1-2).

Conformational and allosteric control  
‐ DDR1 is a constitutive dimer; ligand engagement drives higher-order clustering that enables trans-phosphorylation between neighbouring dimers (juskaite2017collageninducesactivation pages 1-2).  
‐ Disruption of the Asp671–Arg752 clasp shifts the kinase to the DFG-in state, increasing turnover approximately ten-fold (hanson2019whatmakesa pages 3-5).

## Function

Expression: Predominantly in epithelial tissues and organs including lung, brain, kidney, spleen and placenta (mariadoss2023exploringthecellular pages 9-11).  
Ligand binding: Triple-helical collagens I-III, V and IV activate the receptor with slow, sustained kinetics (carafoli2013collagenrecognitionand pages 1-2, juskaite2017collageninducesactivation pages 2-3).  
Downstream signalling: Activated DDR1 engages SRC family kinases and propagates ERK/MAPK, PI3K, JAK/STAT, RAP1 and Notch pathways, up-regulating MMP2, MMP7 and MMP9 to remodel extracellular matrix and facilitate migration (gadiya2018signalingbydiscoidin pages 9-17, kothiwale2015discoidindomainreceptor pages 1-2).  
Mechanical coupling: Phosphorylated Tyr792 promotes association with non-muscle myosin IIA, enhancing force transmission at collagen contacts (coelho2018mechanicalsignalingthrough pages 41-43).

## Inhibitors

Type II (bind DFG-out/allosteric pocket): Imatinib, Nilotinib, Ponatinib; co-crystal structures 4BKJ (imatinib) and 3ZOS (ponatinib) define binding mode (canning2014structuralmechanismsdetermining pages 3-5).  
Type I (bind ATP site while kinase remains DFG-out): Dasatinib, VX-680; kinetic and structural data in PDB 6BSD (dasatinib) and 6BRJ (VX-680) (hanson2019whatmakesa pages 3-5, hanson2019whatmakesa pages 13-15).  
Selective chemical probe: DDR1-IN-1 exploits Thr701 gatekeeper and the hydrophobic allosteric pocket (kothiwale2015discoidindomainreceptor pages 5-6).

## Other Comments

Pathology: DDR1 over-expression or hyper-activation is associated with breast and lung carcinomas, tissue fibrosis, atherosclerosis and osteoarthritis; genetic or pharmacological inhibition reduces disease phenotypes in preclinical models (mariadoss2023exploringthecellular pages 16-18, gadiya2018signalingbydiscoidin pages 9-17).  
Mutations: Missense changes within the kinase core impair catalytic activity and receptor trafficking, contributing to disease pathology (carafoli2013collagenrecognitionand pages 6-7).

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