## Phylogeny

Fibroblast growth factor receptor 2 (FGFR2) is a member of the FGFR family, which consists of four members (FGFR1–FGFR4) exhibiting high sequence homology of 56%-71% (dai2019fibroblastgrowthfactor pages 1-4). Based on Manning et al., FGFRs are classified within the receptor tyrosine kinase (RTK) family (dai2019fibroblastgrowthfactor pages 4-5, lian2024elucidatingtherole pages 1-2). The human RTK superfamily includes over fifty kinases across twenty subfamilies (lian2024elucidatingtherole pages 1-2). The kinase domains of FGFR1 and FGFR2 share approximately 90% sequence identity (lew2007structuralbasisfor pages 3-5).

## Reaction Catalyzed

ATP + [a protein-L-tyrosine] = ADP + [a protein-L-tyrosine phosphate] (dai2019fibroblastgrowthfactor pages 4-5, dai2019fibroblastgrowthfactor pages 1-4, lew2007structuralbasisfor pages 1-2, lian2024elucidatingtherole pages 1-2).

## Cofactor Requirements

The catalytic activity of FGFR2 is Mg2+-dependent (dai2019fibroblastgrowthfactor pages 4-5). Mg2+ ions function as essential cofactors that facilitate the correct orientation and binding of ATP phosphates for the phosphoryl transfer reaction (dai2019fibroblastgrowthfactor pages 4-5, lew2007structuralbasisfor pages 3-5). The conserved aspartate residue of the DFG-motif coordinates these magnesium ions (dai2019fibroblastgrowthfactor pages 4-5).

## Substrate Specificity

The intrinsic substrate specificity of FGFR2 has been experimentally determined using peptide substrate profiling arrays (PSPA) (yaronbarir2024theintrinsicsubstrate pages 2-2, yaronbarir2024theintrinsicsubstrate pages 2-3). Tyrosine kinases, including FGFR2, display strong and diverse preferences for amino acids surrounding the target tyrosine (yaronbarir2024theintrinsicsubstrate pages 15-16). FGFR2 shows strong selectivity for residues at positions −1 to +3 relative to the phosphorylated tyrosine (yaronbarir2024theintrinsicsubstrate pages 15-16). The consensus substrate motif for FGFR2 aligns with preferences for hydrophobic or charged residues in these key positions (yaronbarir2024theintrinsicsubstrate pages 15-16). Substrate recognition is also influenced by basic residues in the kinase catalytic domain that recognize acidic or phosphorylated residues on the substrate (yaronbarir2024theintrinsicsubstrate pages 16-17). Based on hierarchical clustering of motif preferences, FGFR-family kinases cluster together with a unique substrate motif distinct from other RTK families (yaronbarir2024theintrinsicsubstrate pages 2-2).

## Structure

FGFR2 is a single-pass transmembrane receptor composed of three extracellular immunoglobulin-like (Ig-like) domains (D1, D2, and D3), a transmembrane domain, and an intracellular tyrosine kinase domain (TKD) (lian2024elucidatingtherole pages 1-2, dai2019fibroblastgrowthfactor pages 1-4, lew2007structuralbasisfor pages 1-2). The TKD has a bilobed architecture common to protein kinases, with an ATP-binding cleft located between a flexible N-lobe and a more rigid C-lobe (dai2019fibroblastgrowthfactor pages 1-4, dai2019fibroblastgrowthfactor pages 4-5).

Key catalytic and regulatory features of the TKD include: \* **Activation Loop (A-loop):** A key regulatory segment (residues 643–649 and 651–664) that controls kinase activity by switching between inactive and active conformations upon phosphorylation (lian2024elucidatingtherole pages 4-5, lian2024elucidatingtherole pages 2-4). It contains the conserved Asp-Phe-Gly (DFG) motif, which adopts a DFG-in conformation in the active state and a DFG-out conformation in the inactive state (dai2019fibroblastgrowthfactor pages 4-5). \* **Catalytic Pocket:** This region (residues 620–630) forms the enzymatic active site (lian2024elucidatingtherole pages 4-5). It includes the catalytic loop containing the His-Arg-Asp (HRD) motif, where the aspartate residue (Asp-626) acts as the catalytic base for phosphotransfer (dai2019fibroblastgrowthfactor pages 4-5, lew2007structuralbasisfor pages 3-5). \* **P-loop:** A glycine-rich nucleotide-binding loop (residues 480–490) that orients and encloses ATP during catalysis (dai2019fibroblastgrowthfactor pages 4-5, lian2024elucidatingtherole pages 4-5). \* **αC-helix:** Located in the N-lobe (residues 525–539), its orientation is critical for creating a catalytically competent state upon activation (dai2019fibroblastgrowthfactor pages 4-5, lian2024elucidatingtherole pages 2-4). \* **Kinase Hinge and Molecular Brake:** The hinge region (residues 566–571) facilitates domain movement and contains elements of a “molecular brake” that contributes to autoinhibition in the inactive state (lian2024elucidatingtherole pages 4-5, lian2024elucidatingtherole pages 1-2).

Experimentally determined structures are available in the Protein Data Bank, including inactive wild-type (PDB: 1GJO, 2PSQ), active wild-type (PDB: 2PVF), and various disease-associated mutant forms (PDB: 2PVY, 2PWL, 3B2T, 5UGX) (lian2024elucidatingtherole pages 4-5, lian2024elucidatingtherole pages 11-13, lew2007structuralbasisfor pages 5-6).

## Regulation

FGFR2 activation is initiated by ligand-induced dimerization, which promotes trans-autophosphorylation on specific tyrosine residues within the cytoplasmic domain (dai2019fibroblastgrowthfactor pages 1-4, unknownauthors2021characterisationofthe pages 15-21). This autophosphorylation occurs in a sequential and ordered manner on two conserved tyrosine residues in the activation loop, Tyr653 and Tyr654 (unknownauthors2021characterisationofthe pages 15-21, unknownauthors2011theroleof pages 47-53). Phosphorylation of Tyr653 enhances catalytic activity 50- to 100-fold, while subsequent phosphorylation of Tyr654 results in a further 500- to 1000-fold increase in activity (furdui2006autophosphorylationoffgfr1 pages 1-2). These phosphorylation events induce conformational changes that relieve autoinhibition, fully activating the kinase (unknownauthors2021characterisationofthe pages 15-21).

The kinase is maintained in an inactive state by an autoinhibitory mechanism involving a “molecular brake” in the kinase hinge region (lian2024elucidatingtherole pages 1-2, dai2019fibroblastgrowthfactor pages 4-5). FGFR2 exhibits a less stringent autoinhibition mechanism and a faster autophosphorylation rate compared to FGFR1 (lew2007structuralbasisfor pages 1-2). Allosteric regulation occurs via interactions between structural domains, such as the αC-helix and kinase hinge, and can be modulated by peptide mimetics (lian2024elucidatingtherole pages 11-13, katoh2009fgfr2relatedpathogenesisand pages 4-4).

Signaling is negatively regulated by the E3 ubiquitin ligase CBL, which binds to phosphorylated FGFR2 and mediates its ubiquitination (unknownauthors2021characterisationofthe pages 15-21, unknownauthors2013analysisoffgf pages 22-27). This post-translational modification targets the receptor for lysosomal degradation or recycling, thereby attenuating signal duration (unknownauthors2021characterisationofthe pages 15-21, unknownauthors2013analysisoffgf pages 22-27).

## Function

FGFR2 is a receptor tyrosine kinase that plays a vital role in regulating cell proliferation, differentiation, migration, and survival (lian2024elucidatingtherole pages 1-2, dai2019fibroblastgrowthfactor pages 1-4). Alternative splicing generates isoforms with distinct expression patterns; the IIIb isoform is expressed in epithelial cells and the IIIc isoform in mesenchymal cells (lew2007structuralbasisfor pages 1-2).

Upon activation by ligands such as FGF10, FGFR2 phosphorylates downstream signaling molecules including FRS2 and PLCG1 (katoh2009fgfr2relatedpathogenesisand pages 4-4). This initiates signaling cascades, including the MAPK and PLCγ pathways, which modulate targets such as the osteogenesis transcription factor CBFA1 (xie2020fgffgfrsignalingin pages 6-7). Interacting partners recruited to phosphorylated FRS2 include GRB2, GAB1, PIK3R1, and SOS1 (katoh2009fgfr2relatedpathogenesisand pages 4-4).

FGFR2 is essential for embryonic development, particularly for limb outgrowth, lung morphogenesis, and osteogenesis (katoh2009fgfr2relatedpathogenesisand pages 4-4, xie2020fgffgfrsignalingin pages 6-7). In skeletal development, it regulates osteoblast and chondrocyte proliferation and differentiation (xie2020fgffgfrsignalingin pages 6-7). A nuclear form of FGFR2 also contributes to limb development and cell fate determination (xie2020fgffgfrsignalingin pages 6-7).

## Inhibitors

Both small-molecule and RNA-based inhibitors targeting FGFR2 have been developed (lian2024elucidatingtherole pages 1-2, katoh2009fgfr2relatedpathogenesisand pages 4-4). Small molecules often target the ATP-binding site within the kinase domain, with inhibitor-bound structures available (e.g., PDB IDs 4V05, 5JKG) (dai2019fibroblastgrowthfactor pages 4-5). RNA-based therapeutics, such as siRNA, synthetic miRNA, and RNA aptamers, represent an emerging class of inhibitors that block FGFR2 signaling (katoh2009fgfr2relatedpathogenesisand pages 4-4).

## Other Comments

Dysregulation of FGFR2 is associated with developmental disorders and multiple types of cancer (lian2024elucidatingtherole pages 1-2). Depending on the cellular context, FGFR2 can act as either an oncogene or a tumor suppressor (katoh2009fgfr2relatedpathogenesisand pages 4-4).

Disease-associated mutations are frequently gain-of-function and cause constitutive activation by disrupting autoinhibitory mechanisms (lian2024elucidatingtherole pages 1-2). Notable diseases linked to FGFR2 mutations include: \* **Craniosynostosis Syndromes:** Mutations are linked to Apert, Crouzon, and Pfeiffer syndromes (katoh2009fgfr2relatedpathogenesisand pages 4-4, xie2020fgffgfrsignalingin pages 6-7). Specific activating mutations include S252W and P253R in Apert and Crouzon syndromes, and K659N/M/E/Q/T mutations in the activation loop are associated with Crouzon and Pfeiffer syndromes (xie2020fgffgfrsignalingin pages 6-7, lian2024elucidatingtherole pages 11-13). \* **LADD Syndrome (Lacrimo-auriculo-dento-digital syndrome):** Caused by mutations like A628T and A648T that impair kinase activity by altering the catalytic pocket, leading to reduced downstream signaling (lian2024elucidatingtherole pages 16-17, lew2007structuralbasisfor pages 1-2). \* **Cancer:** Somatic mutations are found in endometrial, gastric, colorectal, breast, and lung cancers (katoh2009fgfr2relatedpathogenesisand pages 4-4, lian2024elucidatingtherole pages 1-2). Mutations such as N549H and K659N are observed in endometrial cancer (lian2024elucidatingtherole pages 11-13).

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