Phylogeny  
Fibroblast growth factor receptor 2 (FGFR2) belongs to a four-member FGFR subfamily (FGFR1–FGFR4) that shares 56 – 71 % overall sequence identity; the kinase domains of FGFR1 and FGFR2 are ~90 % identical (Dai et al., 2019; Lew et al., 2007). All FGFRs are classified within the receptor tyrosine kinase (RTK) superfamily, which comprises >50 human kinases distributed among 20 subfamilies (Lian et al., 2024).

Reaction Catalyzed  
ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine phosphate (Dai et al., 2019).

Cofactor Requirements  
Mg²⁺ is essential; it is coordinated by the conserved DFG-motif aspartate and properly orients ATP for phosphoryl transfer (Dai et al., 2019; Lew et al., 2007).

Substrate Specificity  
Peptide-array profiling shows that FGFR2 prefers defined residues at positions −1 to +3 relative to the target Tyr, favouring hydrophobic or charged amino acids (Yaron-Barir et al., 2024). Basic residues within the catalytic domain help recognise acidic or phosphorylated substrate residues. Motif-based clustering groups all FGFR isoforms together and distinguishes them from other RTK families (Yaron-Barir et al., 2024).

Structure  
FGFR2 is a single-pass transmembrane protein containing three extracellular Ig-like domains (D1–D3), a transmembrane helix and a cytoplasmic bilobed tyrosine-kinase domain (TKD) (Lian et al., 2024; Dai et al., 2019).  
Key TKD features include:  
• Activation loop (res. 643–649/651–664) with a DFG motif that toggles between inactive “DFG-out” and active “DFG-in” states.  
• Catalytic loop (res. 620–630) harbouring the HRD motif; Asp626 acts as catalytic base.  
• Glycine-rich P-loop (res. 480–490) that cradles ATP.  
• αC-helix (res. 525–539) whose inward rotation is required for activity.  
• Hinge/molecular brake (res. 566–571) that contributes to autoinhibition.  
Representative PDB entries include inactive (1GJO, 2PSQ), active (2PVF) and disease-associated mutant structures (2PVY, 2PWL, 3B2T, 5UGX) (Lian et al., 2024; Lew et al., 2007).

Regulation  
Ligand binding induces receptor dimerisation and sequential trans-autophosphorylation of Tyr653 followed by Tyr654, producing stepwise 50–100-fold and 500–1000-fold activity increases, respectively (Furdui et al., 2006; Unknown Authors, 2021). Autoinhibition is mediated by a molecular brake in the hinge; FGFR2 is less stringently inhibited and autophosphorylates faster than FGFR1 (Lew et al., 2007; Lian et al., 2024). Allosteric communication between the αC-helix and hinge can be modulated by peptide mimetics (Lian et al., 2024). Signal attenuation occurs via CBL-mediated ubiquitination that targets the receptor for lysosomal degradation or recycling (Unknown Authors, 2021; 2013).

Function  
FGFR2 controls cell proliferation, differentiation, migration and survival (Lian et al., 2024; Dai et al., 2019). Alternative splicing yields an epithelial IIIb and a mesenchymal IIIc isoform (Lew et al., 2007). Upon activation (e.g., by FGF10), FGFR2 phosphorylates FRS2 and PLCG1, initiating MAPK and PLCγ cascades. Phospho-FRS2 recruits GRB2, GAB1, PIK3R1 and SOS1 (Katoh & Katoh, 2009). FGFR2 is indispensable for limb outgrowth, lung branching and osteogenesis; it regulates osteoblast/chondrocyte proliferation and a nuclear receptor form influences limb patterning (Xie et al., 2020).

Inhibitors  
ATP-competitive small molecules bound to the TKD are described (e.g., PDB 4V05, 5JKG) (Dai et al., 2019). RNA-based therapeutics such as siRNA, synthetic miRNA and aptamers are emerging FGFR2 inhibitors (Katoh & Katoh, 2009).

Other Comments  
FGFR2 dysregulation underlies developmental syndromes and diverse cancers. Gain-of-function mutations (e.g., S252W, P253R, K659N) cause Apert, Crouzon or Pfeiffer craniosynostosis; A628T/A648T produce loss-of-function LADD syndrome; somatic variants (e.g., N549H) occur in endometrial, gastric, colorectal, breast and lung tumours (Katoh & Katoh, 2009; Lian et al., 2024; Xie et al., 2020). Depending on context, FGFR2 can act as an oncogene or tumour suppressor (Katoh & Katoh, 2009).

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