## Phylogeny

• Atypical kinase group, FAM20 family within the secretory-pathway kinome (tagliabracci2013phosphorylationofsubstrates pages 1-2)  
• Paralogous expansion generated the pseudokinase FAM20A and glycan-kinase FAM20B from an ancestral metazoan gene (tagliabracci2013phosphorylationofsubstrates pages 2-3)  
• Vertebrate orthologs include Danio rerio drFam20C, Mus musculus Fam20c and Homo sapiens FAM20C (zhang2018structureandevolution pages 3-4)  
• Invertebrate orthologs encompass Caenorhabditis elegans ceFam20 and Drosophila CG31145/Fam20C-like (ishikawa2012therainesyndrome pages 2-3)  
• Drosophila Four-jointed and Hydra hmFam20 represent more distant secretory-kinase relatives (ishikawa2012therainesyndrome pages 2-3)

## Reaction Catalyzed

• ATP + [secreted-protein]-Ser/Thr → ADP + [secreted-protein]-O-phospho-Ser/Thr (ishikawa2012therainesyndrome pages 3-5)

## Cofactor Requirements

• Catalytic activity requires divalent cations with preference Mn²⁺ > Co²⁺ > Mg²⁺ (tagliabracci2013phosphorylationofsubstrates pages 1-2)  
• Sphingosine and sphingosine-1-phosphate act as lipid activators, lowering K\_m^ATP and raising V\_max under Mg²⁺-rich conditions (cozza2015“genuine”caseinkinase pages 9-12)

## Substrate Specificity

• Primary consensus motif: Ser-x-Glu/phospho-Ser (S-x-E/pS) (tagliabracci2013phosphorylationofsubstrates pages 1-2)  
• Extended acidic motifs such as S-x-Q-x-x-D-E-E are also accommodated (xu2021fam20cinhuman pages 1-2)  
• Acidophilic bias; additional downstream Asp/Glu residues enhance recognition (cozza2015“genuine”caseinkinase pages 9-12)  
• Displays negligible activity toward CK1/CK2 consensus peptides, underscoring distinct specificity (ishikawa2012therainesyndrome pages 3-5)

## Structure

• Luminal signal peptide precedes a shell-like kinase fold formed by an N-terminal segment and insertion domain (xu2021fam20cinhuman pages 1-2)  
• Reduced Gly-loop with critical Thr268; Lys285-Glu311 ion pair orients ATP in active site (tagliabracci2013phosphorylationofsubstrates pages 2-3)  
• Variant DNH/AG metal-binding motif and DRHHYE catalytic loop with Asp478 as general base coordinate Mn²⁺ for phosphotransfer (tagliabracci2013phosphorylationofsubstrates pages 2-3)  
• Activation loop is constitutively ordered, supporting continuous catalytic competence (xu2021fam20cinhuman pages 1-2)  
• C-helix engages the Lys-Glu ion pair, maintaining an active conformation without requirement for phosphorylation (tagliabracci2013phosphorylationofsubstrates pages 2-3)  
• Hydrophobic regulatory spine is re-arranged relative to classical kinases, lacking the canonical phenylalanine (tagliabracci2013phosphorylationofsubstrates pages 2-3)  
• Homodimer interface (Phe299-Phe300-Phe354-Pro357 etc.) is essential for activity; dimer-disruptive mutations diminish catalysis (zhang2018structureandevolution pages 3-4)  
• Heterodimer with FAM20A forms a reversed face-to-face interface (~1000 Å²) that allosterically activates FAM20C (zhang2018structureandevolution pages 9-10)  
• Crystal structures: zebrafish Fam20C homodimer (2.2–3.5 Å) and ceFam20 template (PDB 4KQA); Fam20A-Fam20C complex solved using hsFam20A model (PDB 5WRR) (zhang2018structureandevolution pages 9-10)

## Regulation

• Intermolecular autophosphorylation enhances catalytic output (ishikawa2012therainesyndrome pages 2-3)  
• Multiple N-linked glycosylation sites and eight conserved cysteines forming disulfide bonds stabilize the secreted fold (filatova2015theroleof pages 17-20)  
• Homodimerization is required for basal activity; F354A/P357G mutations create a monomeric low-activity enzyme (zhang2018structureandevolution pages 3-4)  
• Heterodimerization with pseudokinase FAM20A elevates k\_cat and rescues certain hypomorphic mutants (cui2015asecretorykinase pages 11-13)  
• ATP binding to FAM20A stabilizes a compact heterodimer conformation that further activates FAM20C (cui2017structureoffam20a pages 6-8)  
• Lipid agonists sphingosine and S1P markedly boost activity under physiological Mg²⁺ (cozza2015“genuine”caseinkinase pages 9-12)  
• Active-site alterations confer resistance to broad-spectrum inhibitor staurosporine (tagliabracci2013phosphorylationofsubstrates pages 1-2)

## Function

• Highly expressed in osteoblasts, odontoblasts, ameloblasts, lactating mammary gland, kidney and parathyroid (cui2015asecretorykinase pages 11-13)  
• Generates the extracellular phosphoproteome by phosphorylating casein and SIBLING proteins within S-x-E/pS motifs (ishikawa2012therainesyndrome pages 6-7)  
• Phosphorylates enamel matrix proteins ENAM, AMBN, AMTN and AMELX, underpinning enamel biomineralization (cui2015asecretorykinase pages 2-4)  
• Phosphorylates and limits bioactive FGF23, thereby controlling systemic phosphate homeostasis (cozza2015“genuine”caseinkinase pages 9-12)  
• Modifies ER oxidoreductases ERO1A and P4HB to bolster proteostasis during ER stress (xu2021fam20cinhuman pages 1-2)  
• Over-expression correlates with tumour progression via extracellular matrix and EMT modulation (wu2021frombiomineralizationto pages 3-5)

## Inhibitors

• Canonical kinase inhibitors such as staurosporine and flavonoids exhibit negligible potency owing to altered ATP pocket geometry (cozza2015“genuine”caseinkinase pages 9-12)

## Other Comments

• Loss-of-function mutations cause lethal and non-lethal Raine syndrome characterized by osteosclerosis and craniofacial anomalies (ishikawa2012therainesyndrome pages 1-2)  
• Hypomorphic alleles Thr268Met and Pro328Ser trigger dental defects and are partially rescued by FAM20A co-expression (cui2015asecretorykinase pages 11-13)  
• Catalytic-site mutations E306Q and D478A abolish activity, leading to FGF23-mediated hypophosphatemic rickets (cozza2015“genuine”caseinkinase pages 9-12)  
• Elevated FAM20C expression is associated with poor prognosis in several cancers (wu2021frombiomineralizationto pages 3-5)

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