## Phylogeny

FAM20A belongs to the Fam20 family of atypical, metazoan-specific secretory pathway kinases (worby2021theabcsof pages 1-2, tagliabracci2013phosphorylationofsubstrates pages 2-3). Due to unique sequence features, the Fam20 family was not included in the original human kinome classification (worby2021theabcsof pages 1-2, sreelatha2015thesecretorypathway pages 1-2). The family includes the paralogs Fam20B and Fam20C (cui2017structureoffam20a pages 1-2). Fam20B is considered the ancestral kinase, from which FAM20A and FAM20C are thought to have arisen by gene duplication (tagliabracci2013phosphorylationofsubstrates pages 2-3, worby2021theabcsof pages 11-12). FAM20A is derived from Fam20C and first appeared in vertebrates; no orthologs have been identified in invertebrates or protochordates (worby2021theabcsof pages 11-12). Fam20 family proteins are conserved in humans, mice, and rats (filatova2015theroleof pages 17-20).

## Reaction Catalyzed

FAM20A is a pseudokinase and is catalytically inactive (cui2015asecretorykinase pages 11-13, cui2017structureoffam20a pages 1-2, filatova2015theroleof pages 20-24). It does not hydrolyze ATP effectively or phosphorylate protein substrates (cui2015asecretorykinase pages 2-4, cui2015asecretorykinase pages 11-13).

## Cofactor Requirements

FAM20A binds ATP in an inverted orientation independently of divalent cations (cui2017structureoffam20a pages 1-2). The substitution of residue Gln258 abolishes manganese binding (worby2021theabcsof pages 7-9).

## Substrate Specificity

FAM20A is a catalytically inactive pseudokinase and does not phosphorylate substrates (cui2015asecretorykinase pages 2-4).

## Structure

FAM20A has an N-terminal signal peptide for entry into the secretory pathway and a C-terminal kinase domain (tagliabracci2013phosphorylationofsubstrates pages 1-2, ishikawa2012therainesyndrome pages 2-3). It is classified as a pseudokinase because it lacks a critical negatively charged residue required for catalytic activity (cui2015asecretorykinase pages 11-13). Specifically, the glutamic acid in the αC helix that forms a key ion pair for kinase activation is replaced by glutamine (Gln258), disrupting this interaction (filatova2015theroleof pages 20-24, sreelatha2015thesecretorypathway pages 6-7). The conformation of its C-helix and activation loop motifs are distinct from canonical kinases, though precise architectural details remain unresolved (worby2021theabcsof pages 1-2, cui2015asecretorykinase pages 11-13). The canonical DFG motif is replaced by a D(N/H)(A/G) motif, and the absence of the phenylalanine residue disrupts the regulatory spine, indicating an inactive conformation (tagliabracci2013phosphorylationofsubstrates pages 2-3).

Crystal structures show that FAM20A forms a reversed face-to-face heterodimer with FAM20C, with an interaction interface of approximately 1000 Å² (zhang2018structureandevolution pages 1-2). Unique structural features include a highly conserved insertion within its Gly-rich loop, an atypical disulfide bond pattern, and an unprecedented inverted ATP-binding mode (cui2017structureoffam20a pages 1-2, cui2017structureoffam20a pages 13-14). The protein surface contains unique hydrophobic residues (Ile214A, Ile255A, and Leu365A) that optimize the interaction with FAM20C (xu2021fam20cinhuman pages 1-2).

## Regulation

N-glycosylation has been identified as a post-translational modification in FAM20A, which is essential for its entry into the secretory pathway, secretion, and stability (worby2021theabcsof pages 1-2). Fam20 kinases contain predicted N-linked glycosylation sites (tagliabracci2013phosphorylationofsubstrates pages 2-3).

The primary regulatory mechanism of FAM20A is allosteric (cui2015asecretorykinase pages 18-18). It functions as an allosteric activator of the kinase FAM20C upon forming a functional complex, which can be a heterodimer or a heterotetramer (cui2015asecretorykinase pages 11-13, zhang2018structureandevolution pages 1-2, filatova2015theroleof pages 20-24). ATP binding to FAM20A, while catalytically incompetent, is thought to stabilize a conformation necessary for this allosteric function (cui2015asecretorykinase pages 11-13).

## Function

FAM20A is expressed in a tissue-specific manner, with high expression in dental tissues (secretory-stage ameloblasts and odontoblasts), the lactating mammary gland, parathyroid gland, kidney, lung, and liver (cui2015asecretorykinase pages 11-13, filatova2015theroleof pages 20-24). Within cells, it is localized to the Golgi apparatus and partially to the endoplasmic reticulum (ishikawa2012therainesyndrome pages 2-3).

The primary function of FAM20A is to act as a regulatory partner for FAM20C (cui2015asecretorykinase pages 2-4). By forming a complex with FAM20C, FAM20A significantly increases FAM20C’s kinase activity toward secreted substrates with SxE motifs (cui2015asecretorykinase pages 11-13). Substrates of the FAM20A/FAM20C complex include enamel matrix proteins such as enamelin (ENAM), amelogenin X (AMELX), ameloblastin (AMBN), and amelotin (AMTN), as well as proteins of the SIBLING family and FGF23 (cui2015asecretorykinase pages 2-4, sreelatha2015thesecretorypathway pages 14-17). This regulatory function is critical for biomineralization processes, including enamel formation and osteoblast mineralization (cui2015asecretorykinase pages 11-13, ohyama2016fam20abindsto pages 5-7). FAM20A also regulates the extracellular accumulation and secretion of FAM20C (ohyama2016fam20abindsto pages 1-2, ohyama2016fam20abindsto pages 5-7).

## Other Comments

Loss-of-function mutations in the FAM20A gene cause Amelogenesis Imperfecta (AI), a hereditary disorder characterized by defective enamel formation (cui2015asecretorykinase pages 11-13, cui2015asecretorykinase pages 2-4). This condition is often part of Enamel-Renal Syndrome (ERS), which can include nephrocalcinosis, gingival hyperplasia, intrapulpal calcifications, and delayed tooth eruption (cui2015asecretorykinase pages 18-18, filatova2015theroleof pages 20-24, cui2017structureoffam20a pages 13-14). These mutations impair the formation or function of the FAM20A/FAM20C complex, leading to inefficient phosphorylation of enamel matrix proteins by FAM20C (cui2015asecretorykinase pages 18-18, cui2015asecretorykinase pages 11-13).

Documented mutations include missense changes (e.g., G331D, D403N, L173R), frameshifts, deletions (e.g., F252del, Q241-R271 deletion), and nonsense mutations (e.g., R243X) that disrupt protein structure, stability, or complex formation (sreelatha2015thesecretorypathway pages 14-17, worby2021theabcsof pages 11-12). A Q258E mutant exhibits a reduced ability to activate FAM20C (cui2015asecretorykinase pages 11-13). Abnormal mRNA splicing leading to the truncation of FAM20A’s unique insertion region also disrupts its function (cui2017structureoffam20a pages 1-2).

References

1. (cui2015asecretorykinase pages 11-13): Jixin Cui, Junyu Xiao, Vincent S Tagliabracci, Jianzhong Wen, Meghdad Rahdar, and Jack E Dixon. A secretory kinase complex regulates extracellular protein phosphorylation. eLife, Mar 2015. URL: https://doi.org/10.7554/elife.06120, doi:10.7554/elife.06120. This article has 125 citations and is from a domain leading peer-reviewed journal.
2. (cui2015asecretorykinase pages 18-18): Jixin Cui, Junyu Xiao, Vincent S Tagliabracci, Jianzhong Wen, Meghdad Rahdar, and Jack E Dixon. A secretory kinase complex regulates extracellular protein phosphorylation. eLife, Mar 2015. URL: https://doi.org/10.7554/elife.06120, doi:10.7554/elife.06120. This article has 125 citations and is from a domain leading peer-reviewed journal.
3. (cui2015asecretorykinase pages 2-4): Jixin Cui, Junyu Xiao, Vincent S Tagliabracci, Jianzhong Wen, Meghdad Rahdar, and Jack E Dixon. A secretory kinase complex regulates extracellular protein phosphorylation. eLife, Mar 2015. URL: https://doi.org/10.7554/elife.06120, doi:10.7554/elife.06120. This article has 125 citations and is from a domain leading peer-reviewed journal.
4. (cui2017structureoffam20a pages 1-2): Jixin Cui, Qinyu Zhu, Hui Zhang, Michael A Cianfrocco, Andres E Leschziner, Jack E Dixon, and Junyu Xiao. Structure of fam20a reveals a pseudokinase featuring a unique disulfide pattern and inverted atp-binding. eLife, Apr 2017. URL: https://doi.org/10.7554/elife.23990, doi:10.7554/elife.23990. This article has 46 citations and is from a domain leading peer-reviewed journal.
5. (cui2017structureoffam20a pages 13-14): Jixin Cui, Qinyu Zhu, Hui Zhang, Michael A Cianfrocco, Andres E Leschziner, Jack E Dixon, and Junyu Xiao. Structure of fam20a reveals a pseudokinase featuring a unique disulfide pattern and inverted atp-binding. eLife, Apr 2017. URL: https://doi.org/10.7554/elife.23990, doi:10.7554/elife.23990. This article has 46 citations and is from a domain leading peer-reviewed journal.
6. (filatova2015theroleof pages 20-24): A. Filatova. The role of fam20a in the generation of amelogenesis imperfecta. Unknown journal, 2015. URL: https://doi.org/10.5167/uzh-121801, doi:10.5167/uzh-121801. This article has 1 citations.
7. (ohyama2016fam20abindsto pages 5-7): Y. Ohyama, Ju-hsien Lin, N. Govitvattana, I. Lin, Sundharamani Venkitapathi, Ahmed Alamoudi, Dina Husein, Chunying An, H. Hotta, M. Kaku, and Yoshiyuki Mochida. Fam20a binds to and regulates fam20c localization. Scientific Reports, Jun 2016. URL: https://doi.org/10.1038/srep27784, doi:10.1038/srep27784. This article has 50 citations and is from a poor quality or predatory journal.
8. (sreelatha2015thesecretorypathway pages 14-17): Anju Sreelatha, Lisa N. Kinch, and Vincent S. Tagliabracci. The secretory pathway kinases. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics, 1854:1687-1693, Oct 2015. URL: https://doi.org/10.1016/j.bbapap.2015.03.015, doi:10.1016/j.bbapap.2015.03.015. This article has 36 citations.
9. (sreelatha2015thesecretorypathway pages 6-7): Anju Sreelatha, Lisa N. Kinch, and Vincent S. Tagliabracci. The secretory pathway kinases. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics, 1854:1687-1693, Oct 2015. URL: https://doi.org/10.1016/j.bbapap.2015.03.015, doi:10.1016/j.bbapap.2015.03.015. This article has 36 citations.
10. (tagliabracci2013phosphorylationofsubstrates pages 1-2): Vincent S. Tagliabracci, Junyu Xiao, and Jack E. Dixon. Phosphorylation of substrates destined for secretion by the fam20 kinases. Biochemical Society transactions, 41 4:1061-5, Aug 2013. URL: https://doi.org/10.1042/bst20130059, doi:10.1042/bst20130059. This article has 26 citations and is from a peer-reviewed journal.
11. (tagliabracci2013phosphorylationofsubstrates pages 2-3): Vincent S. Tagliabracci, Junyu Xiao, and Jack E. Dixon. Phosphorylation of substrates destined for secretion by the fam20 kinases. Biochemical Society transactions, 41 4:1061-5, Aug 2013. URL: https://doi.org/10.1042/bst20130059, doi:10.1042/bst20130059. This article has 26 citations and is from a peer-reviewed journal.
12. (worby2021theabcsof pages 1-2): C. Worby, J. Mayfield, Adam J. Pollak, J. Dixon, and Sourav Banerjee. The abcs of the atypical fam20 secretory pathway kinases. The Journal of Biological Chemistry, Jan 2021. URL: https://doi.org/10.1016/j.jbc.2021.100267, doi:10.1016/j.jbc.2021.100267. This article has 34 citations.
13. (worby2021theabcsof pages 11-12): C. Worby, J. Mayfield, Adam J. Pollak, J. Dixon, and Sourav Banerjee. The abcs of the atypical fam20 secretory pathway kinases. The Journal of Biological Chemistry, Jan 2021. URL: https://doi.org/10.1016/j.jbc.2021.100267, doi:10.1016/j.jbc.2021.100267. This article has 34 citations.
14. (zhang2018structureandevolution pages 1-2): Hui Zhang, Qinyu Zhu, Jixin Cui, Yuxin Wang, Mark J. Chen, Xing Guo, Vincent S. Tagliabracci, Jack E. Dixon, and Junyu Xiao. Structure and evolution of the fam20 kinases. Nature Communications, Mar 2018. URL: https://doi.org/10.1038/s41467-018-03615-z, doi:10.1038/s41467-018-03615-z. This article has 80 citations and is from a highest quality peer-reviewed journal.
15. (filatova2015theroleof pages 17-20): A. Filatova. The role of fam20a in the generation of amelogenesis imperfecta. Unknown journal, 2015. URL: https://doi.org/10.5167/uzh-121801, doi:10.5167/uzh-121801. This article has 1 citations.
16. (ishikawa2012therainesyndrome pages 2-3): Hiroyuki O. Ishikawa, Aiguo Xu, Eri Ogura, Gerard Manning, and Kenneth D. Irvine. The raine syndrome protein fam20c is a golgi kinase that phosphorylates bio-mineralization proteins. PLoS ONE, 7:e42988, Aug 2012. URL: https://doi.org/10.1371/journal.pone.0042988, doi:10.1371/journal.pone.0042988. This article has 176 citations and is from a peer-reviewed journal.
17. (ohyama2016fam20abindsto pages 1-2): Y. Ohyama, Ju-hsien Lin, N. Govitvattana, I. Lin, Sundharamani Venkitapathi, Ahmed Alamoudi, Dina Husein, Chunying An, H. Hotta, M. Kaku, and Yoshiyuki Mochida. Fam20a binds to and regulates fam20c localization. Scientific Reports, Jun 2016. URL: https://doi.org/10.1038/srep27784, doi:10.1038/srep27784. This article has 50 citations and is from a poor quality or predatory journal.
18. (sreelatha2015thesecretorypathway pages 1-2): Anju Sreelatha, Lisa N. Kinch, and Vincent S. Tagliabracci. The secretory pathway kinases. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics, 1854:1687-1693, Oct 2015. URL: https://doi.org/10.1016/j.bbapap.2015.03.015, doi:10.1016/j.bbapap.2015.03.015. This article has 36 citations.
19. (xu2021fam20cinhuman pages 1-2): Rongsheng Xu, Huidan Tan, Jiahui Zhang, Zhaoxin Yuan, Qiang Xie, and Lan Zhang. Fam20c in human diseases: emerging biological functions and therapeutic implications. Frontiers in Molecular Biosciences, Dec 2021. URL: https://doi.org/10.3389/fmolb.2021.790172, doi:10.3389/fmolb.2021.790172. This article has 17 citations and is from a peer-reviewed journal.
20. (worby2021theabcsof pages 7-9): C. Worby, J. Mayfield, Adam J. Pollak, J. Dixon, and Sourav Banerjee. The abcs of the atypical fam20 secretory pathway kinases. The Journal of Biological Chemistry, Jan 2021. URL: https://doi.org/10.1016/j.jbc.2021.100267, doi:10.1016/j.jbc.2021.100267. This article has 34 citations.