## Phylogeny

According to the classification by Manning et al., 2002, Rhodopsin kinase (GRK1) is a Ser-Thr protein kinase belonging to the AGC group of the human kinome and is a member of the G protein-coupled receptor kinase (GRK) family (mushegian2012theoriginand pages 1-2, poulter2021newvariantsand pages 12-12, mushegian2012theoriginand pages 11-11, manning2002theproteinkinase pages 3-3). The GRK family is subdivided into three subfamilies based on sequence homology (hsu2016visualgproteincoupled pages 1-3). GRK1 is part of the GRK1-like subfamily (also referred to as Group I or the GRK1/7 lineage), which includes GRK7 (cone opsin kinase) (hsu2016visualgproteincoupled pages 1-3, zhao1998molecularformsof pages 1-1, mushegian2012theoriginand pages 1-2). Phylogenetic analyses show that vertebrate GRKs form two primary clades: GRK2/3 and a second clade that splits into the GRK1/7 and GRK4/5/6 lineages (mushegian2012theoriginand pages 1-2, mushegian2012theoriginand pages 2-4). GRK1 and GRK7 are closely related, forming a distinct visual subfamily specialized for photoreceptor function (poulter2021newvariantsand pages 12-12).

Orthologs of GRK1 are found in various metazoans, including invertebrates like *Drosophila* and cephalopod mollusks, and in early-branching metazoans such as placozoans, indicating an ancient evolutionary origin (mushegian2012theoriginand pages 1-2, zhao1998molecularformsof pages 1-1, mushegian2012theoriginand pages 12-12). Orthologs are also present in primitive chordates like *Branchiostoma floridae* and *Ciona intestinalis* (mushegian2012theoriginand pages 2-4). Teleost fishes, including zebrafish and carp, have GRK1 paralogs that likely arose from whole-genome duplications (mushegian2012theoriginand pages 4-5). GRKs are proposed to have evolved from the insertion of a kinase domain into an ancestral Regulator of G protein signaling (RGS) domain (mushegian2012theoriginand pages 1-2).

## Reaction Catalyzed

GRK1 is a serine/threonine kinase that catalyzes the ATP-dependent phosphorylation of photo-activated rhodopsin (Metarhodopsin II) (hsu2016visualgproteincoupled pages 1-3, margo2024grk1missensemutations pages 3-4, singh2008structuresofrhodopsin pages 1-2). The chemical reaction involves the transfer of the terminal γ-phosphate from an ATP molecule to the hydroxyl group of specific serine or threonine residues on the activated receptor, yielding ADP and phosphorylated rhodopsin as products (hsu2016visualgproteincoupled pages 3-5, singh2008structuresofrhodopsin pages 4-5, zhao1998molecularformsof pages 1-1).

## Cofactor Requirements

The catalytic activity of GRK1 requires divalent magnesium ions (Mg²⁺) as a cofactor (singh2008structuresofrhodopsin pages 1-2, hsu2016visualgproteincoupled pages 3-5). Mg²⁺ ions are essential for coordinating and stabilizing ATP binding in the active site and facilitating the phosphoryl transfer reaction (hsu2016visualgproteincoupled pages 5-7, singh2008structuresofrhodopsin pages 4-5, singh2008structuresofrhodopsin pages 8-9).

## Substrate Specificity

GRK1 specifically phosphorylates the activated form of rhodopsin (chen2021structuresofrhodopsin pages 19-22). Analysis of substrate specificities for human Ser/Thr kinases indicates that GRK family members exhibit a preference for phosphorylated residues, with a unique selection for the location of phosphorylated threonine or tyrosine within their substrate sequences (johnson2023anatlasof pages 2-3). GRK substrate motifs are influenced by complementary basic residues within their catalytic domains that recognize specific sequence features near the phospho-acceptor site (johnson2023anatlasof pages 2-3). On its primary substrate, rhodopsin, key phosphorylation sites identified on the C-terminus include Ser338, Ser343, and Thr336, with Ser338 and Ser343 being the major sites phosphorylated during the recovery phase of phototransduction (hsu2016visualgproteincoupled pages 3-5, hsu2016visualgproteincoupled pages 3-5).

## Structure

GRK1 is composed of an N-terminal alpha-helical domain, a Regulator of G protein signaling homology (RH) domain, a central protein kinase (PK) domain, and a C-terminal region responsible for lipid binding via prenylation (poulter2021newvariantsand pages 1-2, hsu2016visualgproteincoupled pages 1-3). The RH domain contains a core RGS fold of nine α-helices, supplemented by two GRK-specific helices (singh2008structuresofrhodopsin pages 8-9). The kinase domain has a small lobe (residues 181–268) and a large lobe (residues 269–454), which form the active site cleft (singh2008structuresofrhodopsin pages 5-7, hsu2016visualgproteincoupled pages 5-7). A C-terminal extension (residues 455–511) includes the active site tether (AST; residues 472–480), which contributes to nucleotide binding (hsu2016visualgproteincoupled pages 7-10). Crystal structures of human GRK1 have been solved in multiple ligand-bound and apo states (PDB IDs: 3C4W, 3C4X, 3C4Y, 3C4Z, 3C50, 3C51) (singh2008structuresofrhodopsin pages 1-2).

Key catalytic features include the activation loop (part of the AST), the C-helix (αC-helix), and the hydrophobic spine (singh2008structuresofrhodopsin pages 7-8). In the determined crystal structures, the C-helix and activation loop shape the catalytic core but remain somewhat misaligned for catalysis, suggesting a requirement for receptor-induced conformational changes (singh2008structuresofrhodopsin pages 7-8). The hydrophobic spine, which stabilizes the active conformation in many kinases, appears not to be fully formed in the nucleotide-bound GRK1 structures (singh2008structuresofrhodopsin pages 7-8).

## Regulation

GRK1 activity is modulated by post-translational modifications and allosteric interactions. - **Prenylation**: GRK1 is post-translationally modified by farnesylation at a C-terminal CaaX box, a modification essential for its membrane affinity, correct targeting to photoreceptor outer segments, protein stability, and full kinase activity (hsu2016visualgproteincoupled pages 7-10, hsu2016visualgproteincoupled pages 5-7, mushegian2012theoriginand pages 10-11). Prenyl-binding proteins such as PrBP/δ facilitate this membrane targeting (hsu2016visualgproteincoupled pages 7-10, hsu2016visualgproteincoupled pages 3-5). - **Phosphorylation**: GRK1 undergoes autophosphorylation at C-terminal serine residues (e.g., S488/S489), although this modification is not essential for its activity or for rod recovery kinetics (hsu2016visualgproteincoupled pages 5-7). Additionally, phosphorylation of N-terminal serine residues by protein kinase A (PKA) decreases GRK1 kinase activity (hsu2016visualgproteincoupled pages 5-7). - **Allosteric Regulation**: The calcium-binding protein recoverin (S-modulin) functions as a calcium-dependent inhibitor of GRK1 (hsu2016visualgproteincoupled pages 5-7). At low Ca²⁺ levels, recoverin binds to the N-terminus of GRK1, preventing the conformational changes required for substrate phosphorylation (hsu2016visualgproteincoupled pages 5-7, singh2008structuresofrhodopsin pages 8-9).

## Function

GRK1 is expressed specifically in the retina, primarily in rod photoreceptors but also in cones (hsu2016visualgproteincoupled pages 7-10, hsu2016visualgproteincoupled pages 1-3). Its essential biological function is the phosphorylation of light-activated rhodopsin (metarhodopsin II), which initiates the termination of the phototransduction cascade (poulter2021newvariantsand pages 1-2, hsu2016visualgproteincoupled pages 3-5). This phosphorylation facilitates the high-affinity binding of Arrestin-1 (SAG), which sterically hinders rhodopsin from further activating its G protein, transducin (poulter2021newvariantsand pages 1-2, margo2024grk1missensemutations pages 3-4, hsu2016visualgproteincoupled pages 3-5). This rapid deactivation mechanism is critical for timely photoreceptor recovery and adaptation to changing light conditions (hsu2016visualgproteincoupled pages 7-10). The N-terminus of GRK1 is known to interact with both activated receptors and recoverin (hsu2016visualgproteincoupled pages 7-10).

## Other Comments

Biallelic mutations in the *GRK1* gene, located on chromosome 13q34, are the cause of Oguchi disease, a form of congenital stationary night blindness (poulter2021newvariantsand pages 1-2, margo2024grk1missensemutations pages 3-4). This disease is clinically characterized by severely delayed rod dark adaptation and the Mizuo-Nakamura phenomenon, a distinctive fundus appearance (hsu2016visualgproteincoupled pages 7-10, poulter2021newvariantsand pages 1-2). Identified pathogenic mutations, which often cluster in the kinase domain, impair rhodopsin phosphorylation and prolong the lifetime of the active receptor (poulter2021newvariantsand pages 1-2, hsu2016visualgproteincoupled pages 7-10). Specific examples include the missense mutation P391H, which disrupts the kinase large lobe through steric clashes, and V377D, which is predicted to destabilize the hydrophobic core of the large lobe (singh2008structuresofrhodopsin pages 8-9, poulter2021newvariantsand pages 12-12). A truncation at Ser536 eliminates the C-terminal farnesylation site, causing decreased kinase activity and protein instability (singh2008structuresofrhodopsin pages 8-9). GRK1 knockout mouse models replicate the prolonged rhodopsin activation and delayed photoreceptor recovery seen in patients (hsu2016visualgproteincoupled pages 7-10, hsu2016visualgproteincoupled pages 3-5).

References

1. (hsu2016visualgproteincoupled pages 7-10): Chih-Chun Hsu and Ching-Kang Jason Chen. Visual g protein-coupled receptor kinases. Methods in Pharmacology and Toxicology, pages 45-57, Jan 2016. URL: https://doi.org/10.1007/978-1-4939-3798-1\_3, doi:10.1007/978-1-4939-3798-1\_3. This article has 0 citations.
2. (mushegian2012theoriginand pages 1-2): Arcady Mushegian, Vsevolod V. Gurevich, and Eugenia V. Gurevich. The origin and evolution of g protein-coupled receptor kinases. PLoS ONE, 7:e33806, Mar 2012. URL: https://doi.org/10.1371/journal.pone.0033806, doi:10.1371/journal.pone.0033806. This article has 95 citations and is from a peer-reviewed journal.
3. (mushegian2012theoriginand pages 2-4): Arcady Mushegian, Vsevolod V. Gurevich, and Eugenia V. Gurevich. The origin and evolution of g protein-coupled receptor kinases. PLoS ONE, 7:e33806, Mar 2012. URL: https://doi.org/10.1371/journal.pone.0033806, doi:10.1371/journal.pone.0033806. This article has 95 citations and is from a peer-reviewed journal.
4. (mushegian2012theoriginand pages 4-5): Arcady Mushegian, Vsevolod V. Gurevich, and Eugenia V. Gurevich. The origin and evolution of g protein-coupled receptor kinases. PLoS ONE, 7:e33806, Mar 2012. URL: https://doi.org/10.1371/journal.pone.0033806, doi:10.1371/journal.pone.0033806. This article has 95 citations and is from a peer-reviewed journal.
5. (poulter2021newvariantsand pages 1-2): James A. Poulter, Molly S. C. Gravett, Rachel L. Taylor, Kaoru Fujinami, Julie De Zaeytijd, James Bellingham, Atta Ur Rehman, Takaaki Hayashi, Mineo Kondo, Abdur Rehman, Muhammad Ansar, Dan Donnelly, Carmel Toomes, Manir Ali, Elfride De Baere, Bart P. Leroy, Nigel P. Davies, Robert H. Henderson, Andrew R. Webster, Carlo Rivolta, Christina Zeitz, Omar A. Mahroo, Gavin Arno, Graeme C. M. Black, Martin McKibbin, Sarah A. Harris, Kamron N. Khan, and Chris F. Inglehearn. New variants and in silico analyses in grk1 associated oguchi disease. Human Mutation, 42:164-176, Nov 2021. URL: https://doi.org/10.1002/humu.24140, doi:10.1002/humu.24140. This article has 9 citations and is from a domain leading peer-reviewed journal.
6. (poulter2021newvariantsand pages 12-12): James A. Poulter, Molly S. C. Gravett, Rachel L. Taylor, Kaoru Fujinami, Julie De Zaeytijd, James Bellingham, Atta Ur Rehman, Takaaki Hayashi, Mineo Kondo, Abdur Rehman, Muhammad Ansar, Dan Donnelly, Carmel Toomes, Manir Ali, Elfride De Baere, Bart P. Leroy, Nigel P. Davies, Robert H. Henderson, Andrew R. Webster, Carlo Rivolta, Christina Zeitz, Omar A. Mahroo, Gavin Arno, Graeme C. M. Black, Martin McKibbin, Sarah A. Harris, Kamron N. Khan, and Chris F. Inglehearn. New variants and in silico analyses in grk1 associated oguchi disease. Human Mutation, 42:164-176, Nov 2021. URL: https://doi.org/10.1002/humu.24140, doi:10.1002/humu.24140. This article has 9 citations and is from a domain leading peer-reviewed journal.
7. (hsu2016visualgproteincoupled pages 1-3): Chih-Chun Hsu and Ching-Kang Jason Chen. Visual g protein-coupled receptor kinases. Methods in Pharmacology and Toxicology, pages 45-57, Jan 2016. URL: https://doi.org/10.1007/978-1-4939-3798-1\_3, doi:10.1007/978-1-4939-3798-1\_3. This article has 0 citations.
8. (hsu2016visualgproteincoupled pages 3-5): Chih-Chun Hsu and Ching-Kang Jason Chen. Visual g protein-coupled receptor kinases. Methods in Pharmacology and Toxicology, pages 45-57, Jan 2016. URL: https://doi.org/10.1007/978-1-4939-3798-1\_3, doi:10.1007/978-1-4939-3798-1\_3. This article has 0 citations.
9. (margo2024grk1missensemutations pages 3-4): Theodore Edward Margo, F. Chen, Yu-Jiun Chen, and Ching-Kang Chen. Grk1 missense mutations in type ii oguchi disease: a literature review. Annals of biomedical research, 5 2:1-7, 2024. URL: https://doi.org/10.61545/abr-5-128, doi:10.61545/abr-5-128. This article has 0 citations.
10. (mushegian2012theoriginand pages 10-11): Arcady Mushegian, Vsevolod V. Gurevich, and Eugenia V. Gurevich. The origin and evolution of g protein-coupled receptor kinases. PLoS ONE, 7:e33806, Mar 2012. URL: https://doi.org/10.1371/journal.pone.0033806, doi:10.1371/journal.pone.0033806. This article has 95 citations and is from a peer-reviewed journal.
11. (mushegian2012theoriginand pages 11-11): Arcady Mushegian, Vsevolod V. Gurevich, and Eugenia V. Gurevich. The origin and evolution of g protein-coupled receptor kinases. PLoS ONE, 7:e33806, Mar 2012. URL: https://doi.org/10.1371/journal.pone.0033806, doi:10.1371/journal.pone.0033806. This article has 95 citations and is from a peer-reviewed journal.
12. (mushegian2012theoriginand pages 12-12): Arcady Mushegian, Vsevolod V. Gurevich, and Eugenia V. Gurevich. The origin and evolution of g protein-coupled receptor kinases. PLoS ONE, 7:e33806, Mar 2012. URL: https://doi.org/10.1371/journal.pone.0033806, doi:10.1371/journal.pone.0033806. This article has 95 citations and is from a peer-reviewed journal.
13. (singh2008structuresofrhodopsin pages 4-5): Puja Singh, Benlian Wang, Tadao Maeda, Krzysztof Palczewski, and John J.G. Tesmer. Structures of rhodopsin kinase in different ligand states reveal key elements involved in g protein-coupled receptor kinase activation\*. Journal of Biological Chemistry, 283:14053-14062, May 2008. URL: https://doi.org/10.1074/jbc.m708974200, doi:10.1074/jbc.m708974200. This article has 117 citations and is from a domain leading peer-reviewed journal.
14. (singh2008structuresofrhodopsin pages 5-7): Puja Singh, Benlian Wang, Tadao Maeda, Krzysztof Palczewski, and John J.G. Tesmer. Structures of rhodopsin kinase in different ligand states reveal key elements involved in g protein-coupled receptor kinase activation\*. Journal of Biological Chemistry, 283:14053-14062, May 2008. URL: https://doi.org/10.1074/jbc.m708974200, doi:10.1074/jbc.m708974200. This article has 117 citations and is from a domain leading peer-reviewed journal.
15. (singh2008structuresofrhodopsin pages 7-8): Puja Singh, Benlian Wang, Tadao Maeda, Krzysztof Palczewski, and John J.G. Tesmer. Structures of rhodopsin kinase in different ligand states reveal key elements involved in g protein-coupled receptor kinase activation\*. Journal of Biological Chemistry, 283:14053-14062, May 2008. URL: https://doi.org/10.1074/jbc.m708974200, doi:10.1074/jbc.m708974200. This article has 117 citations and is from a domain leading peer-reviewed journal.
16. (singh2008structuresofrhodopsin pages 8-9): Puja Singh, Benlian Wang, Tadao Maeda, Krzysztof Palczewski, and John J.G. Tesmer. Structures of rhodopsin kinase in different ligand states reveal key elements involved in g protein-coupled receptor kinase activation\*. Journal of Biological Chemistry, 283:14053-14062, May 2008. URL: https://doi.org/10.1074/jbc.m708974200, doi:10.1074/jbc.m708974200. This article has 117 citations and is from a domain leading peer-reviewed journal.
17. (zhao1998molecularformsof pages 1-1): Xinyu Zhao, J. Huang, S. Khani, and K. Palczewski. Molecular forms of human rhodopsin kinase (grk1)\*. The Journal of Biological Chemistry, 273:5124-5131, Feb 1998. URL: https://doi.org/10.1074/jbc.273.9.5124, doi:10.1074/jbc.273.9.5124. This article has 104 citations.
18. (chen2021structuresofrhodopsin pages 19-22): Qiuyan Chen, Manolo Plasencia, Zhuang Li, S. Mukherjee, Dhabaleswar Patra, Chun-Liang Chen, T. Klose, Xin-Qiu Yao, A. Kossiakoff, Leifu Chang, P. Andrews, and J. Tesmer. Structures of rhodopsin in complex with g-protein-coupled receptor kinase 1. Nature, 595:600-605, Jul 2021. URL: https://doi.org/10.1038/s41586-021-03721-x, doi:10.1038/s41586-021-03721-x. This article has 120 citations and is from a highest quality peer-reviewed journal.
19. (hsu2016visualgproteincoupled pages 5-7): Chih-Chun Hsu and Ching-Kang Jason Chen. Visual g protein-coupled receptor kinases. Methods in Pharmacology and Toxicology, pages 45-57, Jan 2016. URL: https://doi.org/10.1007/978-1-4939-3798-1\_3, doi:10.1007/978-1-4939-3798-1\_3. This article has 0 citations.
20. (johnson2023anatlasof pages 2-3): Jared L. Johnson, Tomer M. Yaron, Emily M. Huntsman, Alexander Kerelsky, Junho Song, Amit Regev, Ting-Yu Lin, Katarina Liberatore, Daniel M. Cizin, Benjamin M. Cohen, Neil Vasan, Yilun Ma, Konstantin Krismer, Jaylissa Torres Robles, Bert van de Kooij, Anne E. van Vlimmeren, Nicole Andrée-Busch, Norbert F. Käufer, Maxim V. Dorovkov, Alexey G. Ryazanov, Yuichiro Takagi, Edward R. Kastenhuber, Marcus D. Goncalves, Benjamin D. Hopkins, Olivier Elemento, Dylan J. Taatjes, Alexandre Maucuer, Akio Yamashita, Alexei Degterev, Mohamed Uduman, Jingyi Lu, Sean D. Landry, Bin Zhang, Ian Cossentino, Rune Linding, John Blenis, Peter V. Hornbeck, Benjamin E. Turk, Michael B. Yaffe, and Lewis C. Cantley. An atlas of substrate specificities for the human serine/threonine kinome. Nature, 613:759-766, Jan 2023. URL: https://doi.org/10.1038/s41586-022-05575-3, doi:10.1038/s41586-022-05575-3. This article has 446 citations and is from a highest quality peer-reviewed journal.
21. (manning2002theproteinkinase pages 3-3): G. Manning, D. B. Whyte, R. Martinez, T. Hunter, and S. Sudarsanam. The protein kinase complement of the human genome. Science, 298:1912-1934, Dec 2002. URL: https://doi.org/10.1126/science.1075762, doi:10.1126/science.1075762. This article has 10728 citations and is from a highest quality peer-reviewed journal.
22. (singh2008structuresofrhodopsin pages 1-2): Puja Singh, Benlian Wang, Tadao Maeda, Krzysztof Palczewski, and John J.G. Tesmer. Structures of rhodopsin kinase in different ligand states reveal key elements involved in g protein-coupled receptor kinase activation\*. Journal of Biological Chemistry, 283:14053-14062, May 2008. URL: https://doi.org/10.1074/jbc.m708974200, doi:10.1074/jbc.m708974200. This article has 117 citations and is from a domain leading peer-reviewed journal.