## Phylogeny

G protein-coupled receptor kinase 5 (GRK5) is a eukaryotic Ser/Thr protein kinase classified within the AGC kinase group, which includes PKA, PKG, and PKC (gurevich2012gproteincoupledreceptor pages 1-2, manning2002theproteinkinase pages 2-3, sato2015theevolvingimpact pages 2-3). It belongs to the G protein-coupled receptor kinase (GRK) family, a distinct lineage of kinases that phosphorylate activated G protein-coupled receptors (GPCRs) (gurevich2012gproteincoupledreceptor pages 1-2). Within this family, GRKs are organized into three subfamilies based on sequence similarity and gene structure (gurevich2012gproteincoupledreceptor pages 2-4, sato2015theevolvingimpact pages 2-3). GRK5 is assigned to the GRK4 subfamily, which also contains GRK4 and GRK6 (homan2015crystalstructureof pages 1-2, sato2015theevolvingimpact pages 2-3, gurevich2012gproteincoupledreceptor pages 2-4, dorn2009grkmythologygprotein pages 1-2). Sequence analysis shows that GRK5 shares about 80.7% similarity with GRK4 (premont1994identificationpurificationand pages 3-4). The Drosophila GPRK2 kinase is an ortholog that also clusters phylogenetically within the GRK4/GRK5 subfamily (premont1994identificationpurificationand pages 3-4).

## Reaction Catalyzed

GRK5 is a serine/threonine kinase that catalyzes the transfer of the γ-phosphate group from an ATP molecule to a serine or threonine residue on a protein substrate (chen2024developmentofa pages 1-3). The reaction is: ATP + a protein → ADP + a phosphoprotein (komolov2015atomicstructureof pages 21-22, komolov2015atomicstructureof pages 31-32). Reported kinetic parameters for GRK5 are a Km of approximately 49 µM, a Vmax of approximately 971 nmol Pi/min/mg, and a kcat of approximately 1.10 s⁻¹ (komolov2015atomicstructureof pages 29-31).

## Cofactor Requirements

The catalytic activity of GRK5 requires Mg²⁺ as a cofactor (komolov2015atomicstructureof pages 23-26, komolov2015atomicstructureof pages 29-31).

## Substrate Specificity

Profiling studies of human Ser/Thr kinases show that GRK family kinases, including GRK5, have unique and specific preferences for the location of phosphorylated Thr or Tyr residues within their substrate peptides (johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 2-3). The substrate specificity of GRKs likely involves an initial phospho-priming event by other kinases, followed by GRK-dependent phosphorylation (johnson2023anatlasof pages 2-3). GRK substrate motifs are characterized by this dependence on phosphorylated residues and by selectivity for basic residues in positions surrounding the phospho-acceptor site (johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 2-3). A detailed position-specific scoring matrix (PSSM) or a precise consensus substrate motif for GRK5 is not explicitly provided in the referenced literature (johnson2023anatlasof pages 1-2, johnson2023anatlasof pages 3-4, johnson2023anatlasof pages 6-7).

## Structure

GRK5 is a multi-domain protein containing an N-terminal region, a regulator of G protein signaling (RGS) homology (RH) domain, and a C-terminal region (marzano2021targetinggrk5for pages 2-4, gurevich2012gproteincoupledreceptor pages 2-4). The catalytic kinase domain is bilobal (N-lobe and C-lobe) and is inserted into the RH domain (homan2015crystalstructureof pages 1-2, komolov2015atomicstructureof pages 5-6). Experimentally determined 3D structures are available in the Protein Data Bank under accession codes including 4WNK, 4TND, 4TNB, 8UAP, and 8UAQ (homan2015crystalstructureof pages 1-2, chen2024developmentofa pages 1-3, komolov2015atomicstructureof pages 23-26). - **Activation Loop:** The kinase domain exists in a partially closed, catalytically competent conformation, with the activation loop also in a partially closed state (komolov2015atomicstructureof pages 5-6, komolov2015atomicstructureof pages 7-8). - **Hydrophobic Spine:** A conserved network of hydrophobic residues stabilizes the active conformation by connecting the N- and C-lobes. This spine includes residues Met165, Phe166, and Arg169 from the RH domain, which form a hydrophobic pocket that interacts with Phe527 from the C-terminus (komolov2015atomicstructureof pages 18-20, komolov2015atomicstructureof pages 5-6). - **C-helix:** The αC helix, located in the N-lobe, is crucial for orienting key residues for ATP and substrate binding (komolov2015atomicstructureof pages 5-6). It contains the conserved residue Glu234, which forms a salt bridge with the catalytic Lys215, ensuring its correct positioning (komolov2015atomicstructureof pages 7-8). - **Unique Features:** GRK5 has a highly mobile C-tail that can undergo a conformational shift of 23–26 Å relative to other GRKs (komolov2015atomicstructureof pages 21-22). Unlike other GRKs that can form dimers, GRK5 exists as a monomer, a feature attributed to a unique structural kink in its C-terminus induced by Pro529 (komolov2015atomicstructureof pages 18-20, komolov2015atomicstructureof pages 6-7).

## Regulation

GRK5 activity is regulated by post-translational modifications (PTMs), allosteric interactions, and subcellular localization (komolov2015atomicstructureof pages 13-14). - **Phosphorylation:** GRK5 undergoes intra- and inter-molecular autophosphorylation at sites such as Ser484 and Thr485. These sites are located at the predicted membrane interface, and their phosphorylation negatively regulates GRK5 activity (marzano2021targetinggrk5for pages 2-4, komolov2015atomicstructureof pages 21-22, komolov2015atomicstructureof pages 22-23). GRK5 is also phosphorylated and inhibited by PKC at residues 565–572 (marzano2021targetinggrk5for pages 2-4). - **Allosteric and Conformational Regulation:** The binding of Ca²⁺/Calmodulin (CaM) to sites in both the N-terminal (residues 20–39) and C-terminal (residues 540–578) domains modulates catalytic activity, membrane affinity, and is required for GRK5’s nuclear localization (chen2024developmentofa pages 1-3, marzano2021targetinggrk5for pages 2-4). Interaction with membrane phospholipids, particularly phosphatidylinositol 4,5-bisphosphate (PIP2), is mediated by positively charged residues and an amphipathic helix, which is critical for its membrane localization and function (marzano2021targetinggrk5for pages 2-4, komolov2015atomicstructureof pages 21-22, komolov2015atomicstructureof pages 31-32). Nucleotide binding (ATP or ADP) also provides allosteric stabilization to the protein’s structure (komolov2015atomicstructureof pages 23-26).

## Function

GRK5 is ubiquitously expressed but is found at high levels in the myocardium, prostate, and neuronal tissues. It localizes to the plasma membrane, cytoplasm, and nucleus (chen2024developmentofa pages 1-3, komolov2015atomicstructureof pages 13-14, homan2015crystalstructureof pages 1-2, komolov2015atomicstructureof pages 1-2). - **GPCR Substrates:** The canonical function of GRK5 is the phosphorylation of agonist-bound GPCRs, including adrenergic, muscarinic acetylcholine, dopamine, and opioid receptors. This phosphorylation occurs on intracellular loops and the C-terminal tail, triggering arrestin recruitment and subsequent receptor desensitization and internalization (chen2024developmentofa pages 1-3, homan2015crystalstructureof pages 1-2). - **Non-GPCR Substrates:** GRK5 phosphorylates several non-GPCR proteins. - **TP53/p53:** GRK5 specifically phosphorylates the tumor suppressor p53 at threonine 55 (Thr-55). This modification promotes the interaction between p53 and its E3 ubiquitin ligase, MDM2, leading to p53 ubiquitination and degradation. This action inhibits DNA damage-induced apoptosis (chen2010gproteincoupledreceptorkinase pages 4-5, chen2010gproteincoupledreceptorkinase pages 5-6). Other GRKs, such as GRK2 and GRK6, do not phosphorylate p53 (chen2010gproteincoupledreceptorkinase pages 6-8). - **Arrestin-1 (ARRB1):** GRK5 phosphorylates β-arrestin 1 (also called arrestin-2), which in turn prevents the activation of Src kinase downstream of the 5-HT4 receptor (gurevich2012gproteincoupledreceptor pages 62-63, gurevich2012gproteincoupledreceptor pages 9-10). - **HDAC5:** Phosphorylation of histone deacetylase 5 (HDAC5) by GRK5 causes its export from the nucleus, thereby enabling the transcription of genes associated with cardiac hypertrophy and apoptosis (chen2024developmentofa pages 1-3, chen2010gproteincoupledreceptorkinase pages 5-6). - Other known substrates include the Na+/H+ exchanger regulatory factor (chen2010gproteincoupledreceptorkinase pages 6-8).

## Inhibitors

* **CCG215022:** A rationally designed inhibitor with nanomolar potency against both GRK5 and GRK2 (homan2015crystalstructureof pages 1-2).
* **Sangivamycin:** A nucleoside ATP analog that acts as an inhibitor by binding to the kinase domain of GRK5 (komolov2015atomicstructureof pages 5-6, komolov2015atomicstructureof pages 29-31).
* **Selective Non-covalent Compounds:** A class of potent, non-covalent inhibitors has been developed that shows low nanomolar IC50 values (e.g., 10 nM) and greater than 100,000-fold selectivity for GRK5 over GRK2. Crystal structures of these inhibitors complexed with GRK5 have been solved (PDB IDs 8UAP, 8UAQ) (chen2024developmentofa pages 1-3).

## Other Comments

* **Disease Associations:** GRK5 is implicated in various human pathologies. It is overexpressed in and contributes to cardiovascular diseases, including heart failure, cardiac hypertrophy, dilated cardiomyopathy, and impaired cardiac function after myocardial infarction (chen2024developmentofa pages 1-3, marzano2021targetinggrk5for pages 2-4, lucia2022gproteincoupledreceptor pages 15-15). It is also implicated in several cancers, neurodegenerative disorders like Alzheimer’s disease, and has been associated with susceptibility to type 2 diabetes through genome-wide association studies (chen2024developmentofa pages 1-3, komolov2015atomicstructureof pages 13-14, komolov2015atomicstructureof pages 1-2).
* **Disease Mutations:** A single nucleotide polymorphism (SNP) resulting in a glutamine-to-leucine substitution at position 41 (Q41L) within the RH domain enhances the desensitization of the β2-adrenergic receptor and is associated with a protective effect against congestive heart failure (komolov2015atomicstructureof pages 1-2).

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