## Phylogeny

Protein kinase C γ (PKCγ), encoded by PRKCG, belongs to the PKC family within the AGC kinase group (Manning et al., 2002a; Manning et al., 2002b; Johnson et al., 2023). Within the family it is one of the conventional/classical PKCs (cPKC α, βI, βII, γ) defined by shared cofactor requirements and sequence homology (Shimobayashi, 2016; Grados et al., 2024). PKCγ is conserved across metazoans and shows strong conservation throughout the vertebrate lineage (Manning et al., 2002a; Pilo et al., 2021).

## Reaction Catalyzed

ATP + protein L-Ser/Thr ⇌ ADP + protein O-phospho-L-Ser/Thr (Johnson et al., 2023; Pilo et al., 2021).

## Cofactor Requirements

• Catalytic: Mg²⁺ (Johnson et al., 2023; Pilo et al., 2021)  
• Activation: Ca²⁺ plus lipid cofactors diacylglycerol (DAG) and phosphatidylserine (Johnson et al., 2023; Pilo et al., 2022a; Grados et al., 2024)

## Substrate Specificity

A basophilic kinase (Cluster 1) that favours basic residues (Arg/Lys) at –3/–2 relative to the Ser/Thr phosphoacceptor; frequent consensus motif R-x-x-S/T (Johnson et al., 2023).

## Structure

Modular organisation with an N-terminal regulatory region and a C-terminal kinase domain (Pilo & Newton, 2022).  
• Regulatory region: pseudosubstrate segment (autoinhibition), tandem C1A/C1B DAG-binding domains, Ca²⁺-dependent C2 lipid-binding domain (Pilo et al., 2022a; Pilo & Newton, 2022; Abid et al., 2023).  
• Kinase domain: catalysis (Abid et al., 2023).  
In the inactive state, intramolecular contacts keep the enzyme in a closed, autoinhibited conformation (Pilo & Newton, 2022).

## Regulation

Priming phosphorylations generate a stable but inactive enzyme: PDK1 phosphorylates Thr514 in the activation loop, followed by autophosphorylation of the turn (Thr655) and hydrophobic (Thr674) motifs (Pilo & Newton, 2022; Abid et al., 2023). Binding of Ca²⁺ to the C2 domain and DAG to C1A/C1B triggers membrane translocation, displacement of the pseudosubstrate, and catalytic activation (Pilo et al., 2022a). Mis-autoinhibited molecules are dephosphorylated by PHLPP and degraded via the ubiquitin–proteasome pathway (Pilo et al., 2022a; Shimobayashi & Kapfhammer, 2017).

## Function

Neuron-restricted kinase highly expressed in brain, especially cerebellar Purkinje cells and hippocampus (Grados et al., 2024; Pilo et al., 2022a). Contributes to synaptic plasticity (LTP/LTD) and phosphorylates substrates such as diacylglycerol kinase γ, thereby regulating DAG metabolism (Shimobayashi, 2016; Pilo & Newton, 2022). Participates in MAPK signalling pathways and is positioned by scaffold proteins RACKs and AKAPs (Verbeek et al., 2008; Grados et al., 2024).

## Inhibitors

Phorbol esters act as DAG mimetics to hyper-activate PKCγ but induce prolonged down-regulation and degradation (Pilo et al., 2022a; Pilo & Newton, 2022). C1B-targeted inhibitory peptides reduce cancer cell growth (Pilo & Newton, 2022). Congo red rescues cellular defects caused by mutant PKCγ (Shirafuji et al., 2019).

## Other Comments

Dominant mutations in PRKCG cause spinocerebellar ataxia type 14 (SCA14) (Pilo et al., 2022a; Shirafuji et al., 2019). Most disease variants cluster in C1A/C1B and weaken autoinhibition, elevating basal activity; the extent of autoinhibition loss inversely correlates with age of onset (Pilo & Newton, 2022). Some mutants resist phorbol-ester down-regulation and form amyloid-like aggregates (Shirafuji et al., 2019; Pilo & Newton, 2022).

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