## Phylogeny

PRKY is a human Y-chromosome homolog of the protein kinase PRKX and is a member of the serine/threonine kinase superfamily (li2011prkxcriticallyregulates pages 11-11, johnson2023anatlasof pages 7-7). Based on the kinome classification by Manning et al., PRKY is part of the AGC kinase group and is closely related to the cAMP-dependent protein kinase (PKA) family (huang2016prkxanovel pages 7-7, huang2016prkxanovel pages 2-4). PRKY is a paralog of PRKX, having originated from a gene duplication event and primate chromosome rearrangements (huang2016prkxanovel pages 7-7, huang2016prkxanovel pages 1-2). PRKY shares high sequence similarity (94%) with PRKX, its X-chromosome homolog, indicating a close phylogenetic relationship (huang2016prkxanovel pages 1-2, li2011prkxcriticallyregulates pages 11-11, schiebel1997abnormalxyinterchange pages 2-4).

## Reaction Catalyzed

PRKY catalyzes the phosphotransferase reaction that transfers the γ-phosphate group from ATP to serine or threonine residues on a substrate protein (johnson2023anatlasof pages 7-7).

## Cofactor Requirements

Catalytic activity of PRKY requires the cofactor Mg2+ (johnson2023anatlasof pages 7-7, unknownauthors2021illuminatingunderstudiedkinases pages 25-31).

## Substrate Specificity

A 2023 atlas of substrate specificities for the human serine/threonine kinome provides motifs that define PRKY’s substrate recognition preferences (johnson2023anatlasof pages 7-7). In this study, the kinase (referred to as PRPK) was characterized using peptide substrate libraries to generate position-specific scoring matrices (PSSMs) (johnson2023anatlasof pages 10-11). Prior to this, direct substrate preference motifs for PRKY had not been explicitly characterized, and its substrates were considered unknown (huang2016prkxanovel pages 7-7, huang2016prkxanovel pages 1-2). Based on homology to PRKX and other PKA family members, a preference for basophilic motifs, such as the consensus sequence R-R-X-S/T, was suggested (huang2016prkxanovel pages 7-8, li2011prkxcriticallyregulates pages 11-11).

## Structure

PRKY contains an intact open reading frame with conserved functional domains, including ATP-binding and catalytic domains characteristic of protein kinases (schiebel1997abnormalxyinterchange pages 1-2, schiebel1997abnormalxyinterchange pages 2-4). However, the PRKY protein is 81 amino acids shorter than its homolog PRKX, a truncation resulting from a missing exon (schiebel1997abnormalxyinterchange pages 1-2, schiebel1997abnormalxyinterchange pages 2-4, huang2016prkxanovel pages 1-2). Sources conflict on the availability of 3D structural data; one source from 2025 states that structural data from AlphaFold are available for PRKY (ekhator2025redoxregulationof pages 20-21). In contrast, earlier sources report that structural data for PRKY, including AlphaFold models, are lacking or incomplete (huang2016prkxanovel pages 7-7, li2011prkxcriticallyregulates pages 11-11, huang2016prkxanovel pages 7-8).

## Regulation

The activity and substrate specificity of PRKY are regulated by post-translational modifications (PTMs), which is a common mechanism for kinase regulation (johnson2023anatlasof pages 7-7). Phosphorylation is a key PTM that governs kinase activity (unknownauthors2021illuminatingunderstudiedkinases pages 82-89).

## Function

PRKY expression is predominantly testis-specific, suggesting a role in male germ cell development and reproductive processes (huang2016prkxanovel pages 7-7, li2011prkxcriticallyregulates pages 11-11, huang2016prkxanovel pages 1-2). However, an earlier study also detected PRKY expression in fetal brain and bone marrow cDNA libraries (schiebel1997abnormalxyinterchange pages 1-2, schiebel1997abnormalxyinterchange pages 2-4). Its expression and interaction partners are key to its role in signal transduction pathways, though specific partners are not detailed in the provided context (johnson2023anatlasof pages 7-7).

## Other Comments

Multiple sources describe PRKY as a pseudogene with functional loss due to rearrangements, deletions, and loss of canonical kinase activity (huang2016prkxanovel pages 7-7, ekhator2025redoxregulationof pages 20-21, li2011prkxcriticallyregulates pages 11-11). In direct contrast, the 1997 study that first identified PRKY reported that it is not a pseudogene, as it possesses an intact open reading frame and conserved functional domains, distinguishing it from the actual pseudogene PRKXP1 (schiebel1997abnormalxyinterchange pages 1-2).

Abnormal X-Y interchange and translocation events involving PRKY and its homolog PRKX are implicated in male infertility and disorders of sex development, such as (Y+)XX males and (Y-)XY females (schiebel1997abnormalxyinterchange pages 1-2, huang2016prkxanovel pages 7-7, ekhator2025redoxregulationof pages 20-21). These recombination events account for approximately one-third of such sex reversal cases (schiebel1997abnormalxyinterchange pages 1-2, ekhator2025redoxregulationof pages 20-21).

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