## Proposed EC/sub-subclass

Not specified in the provided Nomenclature.

## Accepted name

AKT serine/threonine-protein kinase 2

## Synonyms

AKT2; Protein kinase B-β (PKBβ)

## Phylogeny

AKT2 is one of three mammalian AKT/PKB isoforms (AKT1/PKBα, AKT2/PKBβ, AKT3/PKBγ). On the basis of kinase-domain homology, it belongs to the AGC kinase group, Akt subfamily (Coffer et al., 1998; Fayard et al., 2005; Kumar & Madison, 2005; Manning & Toker, 2017). Orthologues are conserved from mammals to nematodes and arthropods, including mouse, rat, zebrafish, fruit fly, mosquito and C. elegans (Coffer et al., 1998; Cohen, 2013; Fayard et al., 2005; González & McGraw, 2009).

## Reaction catalysed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + O-phospho-L-seryl/threonyl-[protein] (Coffer et al., 1998).

## Cofactor requirements

Requires Mg²⁺ for catalysis; Mn²⁺ can substitute in some in-vitro assays (Coffer et al., 1998; Barnett et al., 2005; Schultze et al., 2011; Kumar et al., 2025).

## Substrate Specificity

AKT2, like other AKT isoforms, recognises substrates that contain hydrophobic residues N-terminal to the phospho-acceptor site and favours turn-promoting residues (Gly/Asn) at +1. Electrostatic filtering contributes to negative selection against incompatible residues, and phospho-priming at neighbouring positions can enhance recognition (Johnson et al., 2023).

## Structure

AKT2 comprises an N-terminal pleckstrin homology (PH) domain (~1–107), a bilobal kinase domain (~146–440) and a C-terminal hydrophobic-motif tail (Coffer et al., 1998; Schultze et al., 2011; Risso et al., 2015). Crystal structures are available for inactive (PDB 1GZN) and active (PDB 1O6K) kinase-domain conformations (Kumar & Madison, 2005). Activation entails ordering of the activation loop, “DFG-in” realignment, Mg²⁺-ATP coordination by the Asp of the DFG motif and a ~20° lobe rotation (Kumar & Madison, 2005; Lindsley, 2010; Kumar et al., 2025).

## Regulation

• Membrane recruitment via PH-domain binding to PIP₃ generated by PI3K (Schultze et al., 2011; Manning & Toker, 2017).  
• Activating phosphorylations: Thr309 (activation loop) by PDK1 and Ser474 (hydrophobic motif) by mTORC2; sequential phosphorylation yields >100-fold activity increase (Cohen, 2013; Manning & Toker, 2017; Risso et al., 2015).  
• Additional tyrosine phosphorylations (e.g., Tyr316, Tyr323) by Src-family kinases further enhance activity (Risso et al., 2015).  
• Negative regulation: PTEN depletes PIP₃; PP2A and PHLPP dephosphorylate AKT2 (Manning & Toker, 2017; Risso et al., 2015).  
• Other post-translational controls include ubiquitination, SUMOylation, acetylation (e.g., SIRT1-mediated deacetylation of Lys14/Lys20), glycosylation and oxidation (Risso et al., 2015).

## Function

Highly expressed in insulin-responsive tissues (liver, skeletal muscle, adipose) (Schultze et al., 2011; Manning & Toker, 2017). Acts downstream of RTK- and GPCR-stimulated PI3K to regulate cell survival, metabolism, growth and angiogenesis (Coffer et al., 1998; Cohen, 2013). Central to insulin signalling: promotes glucose uptake, glycogen synthesis and suppresses hepatic gluconeogenesis. Key substrates include GSK3, FoxO transcription factors, mTORC1, TBC1D4 and PDE3B (Manning & Toker, 2017).

## Inhibitors

Endogenous antagonists: PTEN (lipid phosphatase), PP2A and PHLPP (protein phosphatases) (Cohen, 2013; Risso et al., 2015). Small-molecule inhibitors include ATP-competitive, allosteric and irreversible AKT-directed compounds; several allosteric agents target the PH domain for isoform selectivity (Barnett et al., 2005; Lindsley, 2010; Nitulescu et al., 2015).

## Other Comments

AKT2 gene (19q13.1-q13.2) amplification or over-expression is common in pancreatic, hepatic and colorectal cancers (Coffer et al., 1998; Cohen, 2013). Germ-line mutations (e.g., p.Glu17Lys, p.Arg274His) are linked to hyperinsulinism, asymmetric overgrowth and severe insulin resistance/type II diabetes (Cohen, 2013; Manning & Toker, 2017).

## References

Barnett, S., Bilodeau, M., & Lindsley, C. (2005). The Akt/PKB family of protein kinases: a review of small molecule inhibitors and progress towards target validation. Current Topics in Medicinal Chemistry, 5, 109–125. https://doi.org/10.2174/1568026053507714

Calleja, V., Laguerre, M., & Larijani, B. (2009). 3-D structure and dynamics of protein kinase B—new mechanism for the allosteric regulation of an AGC kinase. Journal of Chemical Biology, 2, 11–25. https://doi.org/10.1007/s12154-009-0016-8

Coffer, P., Jin, J.-Y., & Woodgett, J. (1998). Protein kinase B (c-Akt): a multifunctional mediator of phosphatidylinositol 3-kinase activation. Biochemical Journal, 335, 1–13. https://doi.org/10.1042/bj3350001

Cohen, M. M. (2013). The Akt genes and their roles in various disorders. American Journal of Medical Genetics Part A, 161, 2931–2937. https://doi.org/10.1002/ajmg.a.36101

Fayard, E., Tintignac, L. A., Baudry, A., & Hemmings, B. A. (2005). Protein kinase B/Akt at a glance. Journal of Cell Science, 118, 5675–5678. https://doi.org/10.1242/jcs.02724

González, E., & McGraw, T. E. (2009). The Akt kinases: isoform specificity in metabolism and cancer. Cell Cycle, 8, 2502–2508. https://doi.org/10.4161/cc.8.16.9335

Johnson, J. L., Yaron, T. M., Huntsman, E. M., Kerelsky, A., Song, J., Regev, A., … Cantley, L. C. (2023). An atlas of substrate specificities for the human serine/threonine kinome. Nature, 613, 759–766. https://doi.org/10.1038/s41586-022-05575-3

Kumar, C., & Madison, V. (2005). Akt crystal structure and Akt-specific inhibitors. Oncogene, 24, 7493–7501. https://doi.org/10.1038/sj.onc.1209087

Kumar, B. H., Kabekkodu, S. P., & Pai, K. S. R. (2025). Structural insights of Akt and its activation mechanism for drug development. Molecular Diversity. https://doi.org/10.1007/s11030-025-11132-7

Lindsley, C. (2010). The Akt/PKB family of protein kinases: a review of small molecule inhibitors and progress towards target validation: a 2009 update. Current Topics in Medicinal Chemistry, 10, 458–477. https://doi.org/10.2174/156802610790980602

Manning, B. D., & Toker, A. (2017). Akt/PKB signaling: navigating the network. Cell, 169, 381–405. https://doi.org/10.1016/j.cell.2017.04.001

Nitulescu, G. M., Margina, D., Juzenas, P., Peng, Q., Olaru, O. T., Saloustros, E., … Tsatsakis, A. M. (2015). Akt inhibitors in cancer treatment: the long journey from drug discovery to clinical use. International Journal of Oncology, 48, 869–885. https://doi.org/10.3892/ijo.2015.3306

Risso, G., Blaustein, M., Pozzi, B., Mammi, P., & Srebrow, A. (2015). Akt/PKB: one kinase, many modifications. Biochemical Journal, 468, 203–214. https://doi.org/10.1042/BJ20150041

Schultze, S., Jensen, J., Hemmings, B., Tschopp, O., & Niessen, M. (2011). Promiscuous affairs of PKB/Akt isoforms in metabolism. Archives of Physiology and Biochemistry, 117, 70–77. https://doi.org/10.3109/13813455.2010.539236