## Phylogeny

BRSK1 (Brain-selective kinase 1; SAD-B) belongs to the AMP-activated protein kinase (AMPK)-related subfamily of serine/threonine protein kinases. Orthologues are present throughout metazoans, including mammals, Caenorhabditis elegans and Drosophila, indicating descent from a common ancestral AMP-activated kinase (Bright et al., 2008).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Bright et al., 2008).

## Cofactor Requirements

Mg²⁺ is essential for ATP coordination and catalysis (Bright et al., 2008).

## Substrate Specificity

Known cellular substrates include CDC25B, CDC25C, MAPT/TAU (Thr 529, Ser 579), RIMS1, γ-tubulins TUBG1 and TUBG2, and WEE1 (Ser 642). Although a strict consensus motif has not been established, BRSK1 targets serine or threonine residues embedded in sequence contexts that support efficient recognition (Bright et al., 2008).

## Structure

The protein comprises:  
• N-terminal kinase domain with GxGxxG glycine-rich loop, VAIK catalytic lysine motif and activation loop Thr 189.  
• Adjacent ubiquitin-associated (UBA) domain that contributes to regulatory conformations.  
• Central proline-rich region.  
• C-terminal KA1 domain containing an autoinhibitory sequence.

An atypical CPE (rather than APE) motif in the activation segment introduces redox-sensitive cysteines capable of forming intramolecular disulfide bonds. AlphaFold and biochemical data show a catalytic core stabilized by a hydrophobic spine and an ordered C-helix, with surrounding regulatory domains modulating activity (Bendzunas et al., 2025).

## Regulation

• Phosphorylation: Constitutively active LKB1 phosphorylates Thr 189 in the activation loop, switching the kinase on (Bright et al., 2008).  
• Redox control: Reducing agents (e.g., DTT) enhance, whereas oxidizing agents (e.g., H₂O₂) inhibit activity through reversible oxidation of conserved cysteines that form disulfide bonds and restrain the catalytic conformation (Bendzunas et al., 2025).

## Function

Enriched in brain tissue, BRSK1 integrates metabolic and redox cues to coordinate:  
• Neuronal polarity and axon specification via MAPT/TAU phosphorylation.  
• Cell-cycle checkpoint responses in neurons through CDC25B/C and WEE1.  
• Centrosome duplication and γ-tubulin complex translocation by modifying TUBG1/TUBG2.  
• Neurotransmitter release by phosphorylating RIMS1.  
Upstream activator: LKB1; downstream effects: modulation of neuronal development, synaptic transmission and cell-cycle control (Bright et al., 2008; Bendzunas et al., 2025).

## Inhibitors

No highly selective inhibitors are currently available. The AMPK-related kinase inhibitor GW296115, which inhibits BRSK2, is suggested as a potential starting point for BRSK1 inhibitor development (Tamir et al., 2020).

## Other Comments

Dysregulation of BRSK1 activity may contribute to neurodegeneration (via aberrant TAU phosphorylation) and to cell-cycle defects. While direct BRSK1 disease mutations are not documented, alterations in the upstream kinase LKB1 are associated with cancer, implicating BRSK1 signaling in related pathologies (Bright et al., 2008; Bendzunas et al., 2025).

## References

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