1. Phylogeny  
   Serine/threonine‐protein kinase BRSK1 is an evolutionarily conserved member of the AMPK‐related kinase family that is ubiquitously found across metazoans, with orthologs in mouse, Caenorhabditis elegans (where it is known as SAD‐1), Drosophila, and ascidians (aguirre2014lkb1ampktsc2signalingpathway pages 56-60). It is grouped within the CAMK family of kinases and forms a subcluster with its close paralog BRSK2 and related MARK kinases, reflecting a conserved role in neuronal polarity and synaptic organization (babot2014regulaciódela pages 221-225). Comparative kinase analyses have positioned BRSK1 within an evolutionary core set of signaling components that emerged early in eukaryotic evolution, consistent with the phylogenetic frameworks reported by Manning and colleagues in landmark studies (lyn2011theregulationof pages 65-70).
2. Reaction Catalyzed  
   BRSK1 catalyzes the transfer of the γ‐phosphate group from ATP to the hydroxyl group of specific serine or threonine residues on substrate proteins, thereby converting ATP to ADP and yielding a phosphorylated substrate plus a proton; the overall reaction is: ATP + [protein] – OH → ADP + [protein] – OPO₃²⁻ + H⁺ (bright2008investigatingtheregulation pages 1-1).
3. Cofactor Requirements  
   Like most serine/threonine kinases, BRSK1 requires Mg²⁺ ions as an essential cofactor to enable the proper binding and orientation of ATP in the catalytic cleft, thereby facilitating effective phosphate transfer (bright2008investigatingtheregulation pages 2-3).
4. Substrate Specificity  
   BRSK1 phosphorylates a defined subset of substrates that play central roles in neuronal polarity and cell cycle regulation; these include the phosphatases CDC25B and CDC25C, the microtubule-associated protein MAPT/TAU, the active zone protein RIMS1, the centrosomal proteins TUBG1 and TUBG2, and the cell cycle regulator WEE1 (aguirre2014lkb1ampktsc2signalingpathway pages 56-60). Substrate specificity studies, such as those reported in the human serine/threonine kinase substrate atlas, indicate that kinases of the CAMK cluster—including BRSK1—often favor consensus sequences with upstream basic residues that help orient the target serine/threonine for phosphorylation (johnson2023anatlasof pages 4-4, banerjee2013phosphorylationubiquitylationand pages 35-39).
5. Structure  
   BRSK1 consists of an N-terminal kinase catalytic domain that contains the conserved motifs required for ATP binding and phosphotransfer, including the glycine-rich loop, the catalytic loop (containing the HRD motif), and the activation (T-) loop (aguirre2014lkb1ampktsc2signalingpathway pages 56-60). Immediately downstream from the kinase domain is a ubiquitin-associated (UBA) domain; although this domain does not mediate ubiquitin binding, it is essential for stabilizing BRSK1’s active conformation and for proper phosphorylation by the upstream kinase LKB1 (babot2014regulaciódela pages 221-225). Current structural models, informed by experimentally derived data and AlphaFold predictions, suggest that BRSK1’s overall 3D organization comprises a conserved kinase core with flanking regulatory regions that modulate substrate access and catalytic efficiency (koduri2024proteinkinasec pages 1-8). The activation loop, which contains the key threonine residue (Thr189 in human BRSK1) that must be phosphorylated for full activity, is a critical regulatory element, and the proper positioning of the C-helix and formation of a hydrophobic spine appear to be necessary for an active kinase conformation (koduri2024proteinkinaseca pages 1-8).
6. Regulation  
   Activation of BRSK1 is primarily achieved through phosphorylation of its activation loop at a conserved threonine residue (Thr189), a modification mediated by the upstream tumor suppressor kinase LKB1 in complex with accessory proteins such as STRAD and MO25 (aguirre2014lkb1ampktsc2signalingpathway pages 56-60, lyn2011theregulationof pages 65-70). In addition to this phosphorylation‐dependent activation, recent studies have demonstrated that BRSK1 activity is subject to redox regulation; reversible oxidative modifications of conserved cysteine residues within the kinase domain can modulate enzyme activity in response to intracellular reactive oxygen species (bendzunas2024redoxregulationof pages 1-3). Alterations in the integrity of the UBA domain also affect the ability of LKB1 to phosphorylate and activate BRSK1, further emphasizing the importance of intramolecular domain interactions (bendzunas2025redoxregulationand pages 2-3). Moreover, BRSK1 can be regulated by additional phosphorylation events; for example, phosphorylation by protein kinase C epsilon (PKCε) at specific serine residues (S555 and S559) has been shown to decrease its enzymatic activity, although such modifications do not appear to impact its subcellular distribution (koduri2024proteinkinaseca pages 13-21).
7. Function  
   BRSK1 plays a critical role in the polarization of neurons by phosphorylating substrates that govern cytoskeletal organization and synaptic vesicle dynamics; for instance, it phosphorylates MAPT/TAU, thereby influencing microtubule stability and neuronal polarity (aguirre2014lkb1ampktsc2signalingpathway pages 56-60). In addition, BRSK1 contributes to the regulation of centrosome duplication by phosphorylating the γ-tubulin isoforms TUBG1 and TUBG2 at Ser131, facilitating their translocation and function in centrosomal organization (aguirre2014lkb1ampktsc2signalingpathway pages 56-60). BRSK1 also modulates cell cycle checkpoints through its activity on key regulators; for example, phosphorylation of WEE1 at Ser642 leads to its down-regulation in postmitotic neurons, while phosphorylation of CDC25B and CDC25C is implicated in the UV-induced DNA damage response (aguirre2014lkb1ampktsc2signalingpathway pages 56-60, lyn2011theregulationofb pages 59-65). Expression of BRSK1 is predominantly restricted to the brain, where it localizes in part to synaptic vesicles, suggesting an additional role in neurotransmitter release via phosphorylation of RIMS1 (babot2014regulaciódela pages 221-225). Its integration in signaling networks downstream of LKB1 further connects BRSK1 to broader pathways controlling neuronal differentiation and genomic stability (tamir2019identificationandcharacterizationa pages 116-120).
8. Other Comments  
   Recent research efforts have highlighted BRSK1 as a potential therapeutic target given its involvement in neuronal development and its association with neurodevelopmental disorders, including autism spectrum disorder (jha2025deeplearningcoupledproximity pages 12-14). Studies have also investigated its role in modulating mTOR and AMPK signaling pathways, linking BRSK1 activity to the regulation of cellular energy stress and protein synthesis (tamir2019identificationandcharacterizationb pages 116-120). Experimental inhibitors that affect kinases within the CAMK family are under preclinical evaluation, and while compounds specifically targeting BRSK1 have been characterized in some studies, issues with selectivity remain a challenge (tamir2020pkisdeepdive pages 14-16). In addition, alterations in BRSK1 function due to genetic variants have been reported, although detailed mutation profiles and their direct functional impacts have not been fully elucidated in the current literature (babot2014regulaciódela pages 221-225). Ongoing research employing RNA interference, CRISPR-mediated gene disruption, and biochemical assays in neuronal models continues to refine our understanding of BRSK1’s role in cell polarity, synaptic function, and checkpoint control (sample2015polarizedactivitiesof pages 13-17).
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