1. Phylogeny  
   BRSK1, also known as SAD-B, is a brain‐selective serine/threonine kinase that belongs to the AMPK‐related kinase family within the CAMK group of the human kinome. Orthologs of BRSK1 have been identified in various species including mouse, Caenorhabditis elegans (where the ortholog is SAD-1), Drosophila, and ascidians, demonstrating its evolutionary conservation across eukaryotes (asiain2012regulaciónyfunción pages 82-89, lyn2011theregulationof pages 65-70). BRSK1 is phylogenetically closely related to its paralog BRSK2, and both kinases share significant sequence conservation within their catalytic domains with other AMPK-related proteins (bendzunas2025redoxregulationand pages 2-3, asiain2012regulaciónyfuncióna pages 82-89).
2. Reaction Catalyzed  
   The catalytic reaction mediated by BRSK1 involves the transfer of a phosphate group from ATP to serine or threonine residues on target substrate proteins. In its reaction, ATP and a protein with a free hydroxyl group are converted to ADP and a phosphorylated protein, releasing a proton in the process (template reaction description; see also aguirre2014lkb1ampktsc2signalingpathway pages 56-60).
3. Cofactor Requirements  
   The kinase activity of BRSK1 depends on the presence of divalent cations, with Mg²⁺ being required as a cofactor to facilitate the transfer of the phosphate group from ATP to the substrate (bright2008investigatingtheregulation pages 1-2).
4. Substrate Specificity  
   BRSK1 phosphorylates a variety of substrates that are critical for neuronal polarity and cell cycle regulation. Its substrates include CDC25B, CDC25C, microtubule-associated protein tau (MAPT/TAU), RIMS1, gamma-tubulin isoforms (TUBG1 and TUBG2), and WEE1. The phosphorylation events occur on serine/threonine residues within target proteins. Although a specific consensus substrate motif is not explicitly defined in the available data, the list of substrates implies that BRSK1 recognizes and phosphorylates specific sequences within proteins that control neuronal polarization and centrosome duplication (banerjee2013phosphorylationubiquitylationanda pages 35-39, tamir2019identificationandcharacterization pages 109-113).
5. Structure  
   BRSK1 is organized into several distinct domains. It contains an N-terminal serine/threonine kinase domain responsible for catalytic activity, which includes critical regulatory elements such as the activation loop (T-loop), where phosphorylation at a conserved threonine residue (Thr-189) is essential for activation by upstream kinases like LKB1 (asiain2012regulaciónyfunción pages 82-89, bright2008investigatingtheregulation pages 7-8). Adjacent to the kinase domain is a ubiquitin-associated (UBA) domain, which is thought to contribute to structural stabilization and possibly to regulate the conformational state of the kinase. Further downstream, BRSK1 possesses regulatory regions that may include proline-rich sequences and a kinase-associated (KA1) domain along with an autoinhibitory sequence (AIS) at the C-terminus; these domains have been described in the context of the broader AMPK-related protein family (tamir2019identificationandcharacterization pages 109-113). Unique structural features of BRSK1 also include redox-sensitive cysteine residues in the kinase domain that mediate reversible oxidative modifications, thereby serving as redox sensors that modulate kinase activity (bendzunas2024redoxregulationof pages 3-7, bendzunas2025redoxregulationand pages 7-9).
6. Regulation  
   BRSK1 is regulated at multiple levels through phosphorylation, lipid modification, and redox-dependent mechanisms. Its full activation is dependent on phosphorylation of a conserved threonine residue (Thr-189) in the activation loop by the upstream kinase LKB1, which is essential for its catalytic activation in neurons and other cell types (aguirre2014lkb1ampktsc2signalingpathway pages 56-60, lyn2011theregulationofa pages 65-70). In addition, BRSK1 activity is modulated by post-translational modifications such as palmitoylation; this lipid modification promotes association with membrane lipid rafts in neurons, which is linked to increased kinase activity and enhanced T-loop phosphorylation (asiain2012regulaciónyfunción pages 82-89, babot2014regulaciódela pages 221-225). Redox regulation also plays a significant role; reversible oxidative modifications of conserved cysteine residues within the kinase domain, including those forming intramolecular disulfide bonds, can alter the catalytic activity of BRSK1 in response to cellular redox changes (bendzunas2024redoxregulationof pages 15-18, bendzunas2025redoxregulationand pages 14-15). Moreover, phosphorylation by Protein Kinase C epsilon on serine residues (S555 and S559) has been shown to negatively regulate BRSK1 activity without affecting its subcellular localization (koduri2024proteinkinasec pages 13-21, koduri2024proteinkinasecb pages 13-21).
7. Function  
   BRSK1 plays a central role in neuronal polarization and centrosome duplication. In cortical neurons, following activation by LKB1, BRSK1 phosphorylates microtubule-associated protein tau at residues including Thr-529 and Ser-579, which is implicated in the establishment of neuronal polarity (aguirre2014lkb1ampktsc2signalingpathway pages 56-60, lyn2011theregulationofa pages 65-70). Additionally, BRSK1 phosphorylates WEE1 at Ser-642 in postmitotic neurons, leading to the down-regulation of WEE1 kinase activity—a key regulatory step in neuronal polarization (aguirre2014lkb1ampktsc2signalingpathway pages 56-60). Beyond its roles in neuronal differentiation, BRSK1 is involved in centrosome duplication where it phosphorylates gamma-tubulin isoforms (TUBG1 and TUBG2) at Ser-131; this phosphorylation promotes the translocation of gamma-tubulin and its associated proteins to the centrosome, thereby positively regulating centrosome duplication (aguirre2014lkb1ampktsc2signalingpathway pages 56-60). BRSK1 is also localized to synaptic vesicles within neurons, potentially influencing neurotransmitter release through phosphorylation of synaptic regulatory proteins such as RIMS1 (asiain2012regulaciónyfunciónc pages 82-89, babot2014regulaciódela pages 231-232). In the context of DNA damage response, BRSK1 participates in the UV-induced checkpoint response by modulating CDK1 activity through phosphorylation and activation of WEE1 and inhibition of CDC25B and CDC25C (aguirre2014lkb1ampktsc2signalingpathway pages 56-60).
8. Other Comments  
   While specific chemical inhibitors for BRSK1 have not been detailed in the provided literature, its critical roles in neuronal polarization, centrosome duplication, and DNA damage checkpoint response make it a potential target for therapeutic intervention in neurodevelopmental disorders and cancers associated with dysregulated LKB1 signaling (banerjee2013phosphorylationubiquitylationanda pages 35-39, peart2014distinctrolesofa pages 70-73). No extensive data regarding disease-causing mutations in BRSK1 are provided in the current context; however, alterations in upstream regulators such as LKB1, which directly activates BRSK1, have been associated with tumor suppressor functions and could impact BRSK1 activity (henriksson2012lkb1signalingpathwaysb pages 30-33).
9. References  
   aguirre2014lkb1ampktsc2signalingpathway pages 56-60;  
   asiain2012regulaciónyfunción pages 82-89;  
   asiain2012regulaciónyfuncióna pages 82-89;  
   asiain2012regulaciónyfunciónb pages 82-89;  
   asiain2012regulaciónyfunciónc pages 82-89;  
   babot2014regulaciódela pages 221-225;  
   banerjee2013phosphorylationubiquitylationanda pages 35-39;  
   bendzunas2024redoxregulationof pages 3-7;  
   bendzunas2024redoxregulationof pages 15-18;  
   bendzunas2025redoxregulationand pages 2-3;  
   bendzunas2025redoxregulationand pages 14-15;  
   bendzunas2025redoxregulationand pages 26-26;  
   bendzunas2025redoxregulationand pages 5-7;  
   bendzunas2025redoxregulationand pages 7-9;  
   bright2008investigatingtheregulation pages 1-1;  
   bright2008investigatingtheregulation pages 1-2;  
   bright2008investigatingtheregulation pages 6-7;  
   bright2008investigatingtheregulation pages 7-8;  
   bright2008investigatingtheregulation pages 8-9;  
   guo2006brsk2isactivated pages 1-2;  
   guo2006brsk2isactivated pages 4-5;  
   koduri2024proteinkinasec pages 13-21;  
   koduri2024proteinkinasecb pages 13-21;  
   lyn2011theregulationof pages 59-65;  
   lyn2011theregulationofa pages 65-70;  
   lyn2011theregulationofb pages 65-70;  
   walkinshaw2011histonedeacetylaseregulation pages 47-52;  
   walkinshaw2011histonedeacetylaseregulationa pages 47-52;  
   henriksson2012lkb1signalingpathwaysa pages 30-33;  
   henriksson2012lkb1signalingpathwaysb pages 30-33;  
   jha2025deeplearningcoupledproximity pages 12-14;  
   jha2025deeplearningcoupledproximity pages 24-26;  
   li2012apcccdh1targetsbrainspecific pages 5-8;  
   molina2021ampkαlikeproteinsas pages 1-3;  
   peart2014distinctrolesofa pages 70-73;  
   sample2015polarizedactivitiesof pages 4-7;  
   tamir2019identificationandcharacterization pages 109-113.

References

1. (aguirre2014lkb1ampktsc2signalingpathway pages 56-60): I de Aguirre. Lkb1/ampk/tsc2 signaling pathway alterations in non-small-cell-lung-carcinoma. Unknown journal, 2014.
2. (asiain2012regulaciónyfunción pages 82-89): A Rodríguez Asiain. Regulación y función de las brain-specific kinases 1 y 2 (brsk1 y brsk2, también llamadas sad quinasas) en la diferenciación y sinapsis neuronales. Unknown journal, 2012.
3. (asiain2012regulaciónyfuncióna pages 82-89): A Rodríguez Asiain. Regulación y función de las brain-specific kinases 1 y 2 (brsk1 y brsk2, también llamadas sad quinasas) en la diferenciación y sinapsis neuronales. Unknown journal, 2012.
4. (asiain2012regulaciónyfunciónb pages 82-89): A Rodríguez Asiain. Regulación y función de las brain-specific kinases 1 y 2 (brsk1 y brsk2, también llamadas sad quinasas) en la diferenciación y sinapsis neuronales. Unknown journal, 2012.
5. (asiain2012regulaciónyfunciónc pages 82-89): A Rodríguez Asiain. Regulación y función de las brain-specific kinases 1 y 2 (brsk1 y brsk2, también llamadas sad quinasas) en la diferenciación y sinapsis neuronales. Unknown journal, 2012.
6. (babot2014regulaciódela pages 221-225): G Ruiz Babot. Regulació de la brain-specific kinase 1 (brsk1) neuronal per sulfàtid i modificacions post-traduccionals. Unknown journal, 2014.
7. (banerjee2013phosphorylationubiquitylationanda pages 35-39): S Banerjee. Phosphorylation, ubiquitylation and characterisation of specific inhibitors of ampk-related kinase nuak1/ark5. Unknown journal, 2013.
8. (bendzunas2024redoxregulationof pages 3-7): George N. Bendzunas, Dominic P Byrne, Safal Shrestha, Leonard A Daly, Sally O. Oswald, Samiksha Katiyar, Aarya Venkat, Wayland Yeung, Claire E Eyers, Patrick A Eyers, and Natarajan Kannan. Redox regulation of brain selective kinases brsk1/2: implications for dynamic control of the eukaryotic ampk family through cys-based mechanisms. bioRxiv, Apr 2024. URL: https://doi.org/10.7554/elife.92536.2, doi:10.7554/elife.92536.2. This article has 6 citations.
9. (bendzunas2025redoxregulationand pages 2-3): George N Bendzunas, Dominic P Byrne, Safal Shrestha, Leonard A Daly, Sally O Oswald, Samiksha Katiyar, Aarya Venkat, Wayland Yeung, Claire E Eyers, Patrick A Eyers, and Natarajan Kannan. Redox regulation and dynamic control of brain-selective kinases brsk1/2 in the ampk family through cysteine-based mechanisms. eLife, Apr 2025. URL: https://doi.org/10.7554/elife.92536.4, doi:10.7554/elife.92536.4. This article has 0 citations and is from a domain leading peer-reviewed journal.
10. (bendzunas2025redoxregulationand pages 26-26): George N Bendzunas, Dominic P Byrne, Safal Shrestha, Leonard A Daly, Sally O Oswald, Samiksha Katiyar, Aarya Venkat, Wayland Yeung, Claire E Eyers, Patrick A Eyers, and Natarajan Kannan. Redox regulation and dynamic control of brain-selective kinases brsk1/2 in the ampk family through cysteine-based mechanisms. eLife, Apr 2025. URL: https://doi.org/10.7554/elife.92536.4, doi:10.7554/elife.92536.4. This article has 0 citations and is from a domain leading peer-reviewed journal.
11. (bright2008investigatingtheregulation pages 1-1): Nicola J. Bright, David Carling, and Claire Thornton. Investigating the regulation of brain-specific kinases 1 and 2 by phosphorylation. Journal of Biological Chemistry, 283:14946-14954, May 2008. URL: https://doi.org/10.1074/jbc.m710381200, doi:10.1074/jbc.m710381200. This article has 67 citations and is from a domain leading peer-reviewed journal.
12. (bright2008investigatingtheregulation pages 6-7): Nicola J. Bright, David Carling, and Claire Thornton. Investigating the regulation of brain-specific kinases 1 and 2 by phosphorylation. Journal of Biological Chemistry, 283:14946-14954, May 2008. URL: https://doi.org/10.1074/jbc.m710381200, doi:10.1074/jbc.m710381200. This article has 67 citations and is from a domain leading peer-reviewed journal.
13. (guo2006brsk2isactivated pages 4-5): Zekun Guo, Wenwen Tang, Jian Yuan, Xinya Chen, Bo Wan, Xiuting Gu, Kuntian Luo, Yingli Wang, and Long Yu. Brsk2 is activated by cyclic amp-dependent protein kinase a through phosphorylation at thr260. Biochemical and Biophysical Research Communications, 347:867-871, Sep 2006. URL: https://doi.org/10.1016/j.bbrc.2006.06.178, doi:10.1016/j.bbrc.2006.06.178. This article has 21 citations and is from a peer-reviewed journal.
14. (koduri2024proteinkinasec pages 13-21): A Koduri. Protein kinase c epsilon regulation of brain-specific serine/threonine-protein kinase 1 kinase activity and nuclear localization. Unknown journal, 2024.
15. (koduri2024proteinkinasecb pages 13-21): A Koduri. Protein kinase c epsilon regulation of brain-specific serine/threonine-protein kinase 1 kinase activity and nuclear localization. Unknown journal, 2024.
16. (lyn2011theregulationof pages 59-65): CL Lyn. The regulation of tau-dependent neurodegeneration by brain selective/sad kinases. Unknown journal, 2011.
17. (lyn2011theregulationof pages 65-70): CL Lyn. The regulation of tau-dependent neurodegeneration by brain selective/sad kinases. Unknown journal, 2011.
18. (lyn2011theregulationofa pages 65-70): CL Lyn. The regulation of tau-dependent neurodegeneration by brain selective/sad kinases. Unknown journal, 2011.
19. (lyn2011theregulationofb pages 65-70): CL Lyn. The regulation of tau-dependent neurodegeneration by brain selective/sad kinases. Unknown journal, 2011.
20. (walkinshaw2011histonedeacetylaseregulation pages 47-52): DR Walkinshaw. Histone deacetylase regulation by lkb1 and pka signaling pathways. Unknown journal, 2011.
21. (walkinshaw2011histonedeacetylaseregulationa pages 47-52): DR Walkinshaw. Histone deacetylase regulation by lkb1 and pka signaling pathways. Unknown journal, 2011.
22. (babot2014regulaciódela pages 231-232): G Ruiz Babot. Regulació de la brain-specific kinase 1 (brsk1) neuronal per sulfàtid i modificacions post-traduccionals. Unknown journal, 2014.
23. (bendzunas2024redoxregulationof pages 15-18): George N. Bendzunas, Dominic P Byrne, Safal Shrestha, Leonard A Daly, Sally O. Oswald, Samiksha Katiyar, Aarya Venkat, Wayland Yeung, Claire E Eyers, Patrick A Eyers, and Natarajan Kannan. Redox regulation of brain selective kinases brsk1/2: implications for dynamic control of the eukaryotic ampk family through cys-based mechanisms. bioRxiv, Apr 2024. URL: https://doi.org/10.7554/elife.92536.2, doi:10.7554/elife.92536.2. This article has 6 citations.
24. (bendzunas2025redoxregulationand pages 14-15): George N Bendzunas, Dominic P Byrne, Safal Shrestha, Leonard A Daly, Sally O Oswald, Samiksha Katiyar, Aarya Venkat, Wayland Yeung, Claire E Eyers, Patrick A Eyers, and Natarajan Kannan. Redox regulation and dynamic control of brain-selective kinases brsk1/2 in the ampk family through cysteine-based mechanisms. eLife, Apr 2025. URL: https://doi.org/10.7554/elife.92536.4, doi:10.7554/elife.92536.4. This article has 0 citations and is from a domain leading peer-reviewed journal.
25. (bendzunas2025redoxregulationand pages 5-7): George N Bendzunas, Dominic P Byrne, Safal Shrestha, Leonard A Daly, Sally O Oswald, Samiksha Katiyar, Aarya Venkat, Wayland Yeung, Claire E Eyers, Patrick A Eyers, and Natarajan Kannan. Redox regulation and dynamic control of brain-selective kinases brsk1/2 in the ampk family through cysteine-based mechanisms. eLife, Apr 2025. URL: https://doi.org/10.7554/elife.92536.4, doi:10.7554/elife.92536.4. This article has 0 citations and is from a domain leading peer-reviewed journal.
26. (bendzunas2025redoxregulationand pages 7-9): George N Bendzunas, Dominic P Byrne, Safal Shrestha, Leonard A Daly, Sally O Oswald, Samiksha Katiyar, Aarya Venkat, Wayland Yeung, Claire E Eyers, Patrick A Eyers, and Natarajan Kannan. Redox regulation and dynamic control of brain-selective kinases brsk1/2 in the ampk family through cysteine-based mechanisms. eLife, Apr 2025. URL: https://doi.org/10.7554/elife.92536.4, doi:10.7554/elife.92536.4. This article has 0 citations and is from a domain leading peer-reviewed journal.
27. (bright2008investigatingtheregulation pages 1-2): Nicola J. Bright, David Carling, and Claire Thornton. Investigating the regulation of brain-specific kinases 1 and 2 by phosphorylation. Journal of Biological Chemistry, 283:14946-14954, May 2008. URL: https://doi.org/10.1074/jbc.m710381200, doi:10.1074/jbc.m710381200. This article has 67 citations and is from a domain leading peer-reviewed journal.
28. (bright2008investigatingtheregulation pages 7-8): Nicola J. Bright, David Carling, and Claire Thornton. Investigating the regulation of brain-specific kinases 1 and 2 by phosphorylation. Journal of Biological Chemistry, 283:14946-14954, May 2008. URL: https://doi.org/10.1074/jbc.m710381200, doi:10.1074/jbc.m710381200. This article has 67 citations and is from a domain leading peer-reviewed journal.
29. (bright2008investigatingtheregulation pages 8-9): Nicola J. Bright, David Carling, and Claire Thornton. Investigating the regulation of brain-specific kinases 1 and 2 by phosphorylation. Journal of Biological Chemistry, 283:14946-14954, May 2008. URL: https://doi.org/10.1074/jbc.m710381200, doi:10.1074/jbc.m710381200. This article has 67 citations and is from a domain leading peer-reviewed journal.
30. (guo2006brsk2isactivated pages 1-2): Zekun Guo, Wenwen Tang, Jian Yuan, Xinya Chen, Bo Wan, Xiuting Gu, Kuntian Luo, Yingli Wang, and Long Yu. Brsk2 is activated by cyclic amp-dependent protein kinase a through phosphorylation at thr260. Biochemical and Biophysical Research Communications, 347:867-871, Sep 2006. URL: https://doi.org/10.1016/j.bbrc.2006.06.178, doi:10.1016/j.bbrc.2006.06.178. This article has 21 citations and is from a peer-reviewed journal.
31. (henriksson2012lkb1signalingpathwaysa pages 30-33): E Henriksson. Lkb1 signaling pathways in adipocytes-focus on the ampk-related kinase sik2. Unknown journal, 2012.
32. (henriksson2012lkb1signalingpathwaysb pages 30-33): E Henriksson. Lkb1 signaling pathways in adipocytes-focus on the ampk-related kinase sik2. Unknown journal, 2012.
33. (jha2025deeplearningcoupledproximity pages 12-14): Kanchan Jha, Daichi Shonai, Aditya Parekh, Akiyoshi Uezu, Tomoyuki Fujiyama, Hikari Yamamoto, Pooja Parameswaran, Masashi Yanagisawa, Rohit Singh, and Scott H. Soderling. Deep learning-coupled proximity proteomics to deconvolve kinase signaling in vivo. BioRxiv, Apr 2025. URL: https://doi.org/10.1101/2025.04.27.650849, doi:10.1101/2025.04.27.650849. This article has 0 citations.
34. (jha2025deeplearningcoupledproximity pages 24-26): Kanchan Jha, Daichi Shonai, Aditya Parekh, Akiyoshi Uezu, Tomoyuki Fujiyama, Hikari Yamamoto, Pooja Parameswaran, Masashi Yanagisawa, Rohit Singh, and Scott H. Soderling. Deep learning-coupled proximity proteomics to deconvolve kinase signaling in vivo. BioRxiv, Apr 2025. URL: https://doi.org/10.1101/2025.04.27.650849, doi:10.1101/2025.04.27.650849. This article has 0 citations.
35. (li2012apcccdh1targetsbrainspecific pages 5-8): Ruwei Li, Bo Wan, Jun Zhou, Yingli Wang, Ting Luo, Xiuting Gu, Fang Chen, and Long Yu. Apc/ccdh1 targets brain-specific kinase 2 (brsk2) for degradation via the ubiquitin-proteasome pathway. PLoS ONE, 7:e45932, Sep 2012. URL: https://doi.org/10.1371/journal.pone.0045932, doi:10.1371/journal.pone.0045932. This article has 15 citations and is from a peer-reviewed journal.
36. (molina2021ampkαlikeproteinsas pages 1-3): Ester Molina, Linda J Hong, and IIana Chefetz. Ampkα-like proteins as lkb1 downstream targets in cell physiology and cancer. Journal of Molecular Medicine, 99:651-662, Mar 2021. URL: https://doi.org/10.1007/s00109-021-02040-y, doi:10.1007/s00109-021-02040-y. This article has 24 citations.
37. (peart2014distinctrolesofa pages 70-73): TM Peart. Distinct roles of bmp and lkb1/ampk signalling impacting ovarian cancer spheroid biology. Unknown journal, 2014.
38. (sample2015polarizedactivitiesof pages 4-7): Vedangi Sample, Santosh Ramamurthy, Kirill Gorshkov, Gabriele V. Ronnett, and Jin Zhang. Polarized activities of ampk and brsk in primary hippocampal neurons. Molecular Biology of the Cell, 26:1935-1946, May 2015. URL: https://doi.org/10.1091/mbc.e14-02-0764, doi:10.1091/mbc.e14-02-0764. This article has 41 citations and is from a domain leading peer-reviewed journal.
39. (tamir2019identificationandcharacterization pages 109-113): TY Tamir. Identification and characterization of kinase regulators in keap1/nrf2 signaling. Unknown journal, 2019.