## Phylogeny

Orthologs of TRIB2 are present in basal metazoans such as the sponge Amphimedon queenslandica and the cnidarian Nematostella vectensis, are retained in protostomes including Drosophila melanogaster, and occur across all surveyed vertebrate classes (eyers2017tribblesinthe pages 2-4).  
Comparative analyses identify TRIB2 as the most ancestral paralog within the mammalian Tribbles family, predating the emergence of TRIB1 and TRIB3 (eyers2017tribblesinthe pages 1-2).  
Kinome mapping places TRIB2 in the Ca²⁺/calmodulin-dependent protein kinase (CAMK) group, Tribbles pseudokinase subfamily, which is distinguished from catalytically active CAMKs by loss of canonical catalytic motifs (lohan2013thefunctionallydiverse pages 1-2).

## Reaction Catalyzed

ATP + protein ⇄ ADP + phosphoprotein; however, no measurable phosphotransferase activity has been detected, classifying TRIB2 as a pseudokinase (richmond2020pseudokinasesatribble‐edged pages 1-2).

## Cofactor Requirements

Biochemical assays fail to detect Mg²⁺-dependent ATP binding in the pseudokinase domain (jamieson2022nanobodiesidentifyan pages 12-15).

## Substrate Specificity

No substrates or consensus phosphorylation motif are reported for TRIB2 in current kinase-substrate atlases (jamieson2022nanobodiesidentifyan pages 4-8).

## Structure

Domain organisation: N-terminal PEST/Degradation region (residues 1–60) controlling protein half-life; central bilobed pseudokinase domain (64–308) with atypical EGDHVF glycine-rich loop, truncated αC-helix, conserved β3 Lys90, and ESLED motif replacing the canonical DFG triad; C-terminal tail (309–343) containing ILDHPWF MAPK-docking sequence and DQLVPD E3-ligase binding degron (mayoralvaro2021thecriticalrole pages 2-4).  
Three-dimensional data: A 2.7 Å crystal structure of the pseudokinase core complexed with nanobody Nb4.103 (PDB 8O6V) reveals a bent αC-helix, an ordered open activation loop and an ATP-incompetent pseudo-active site (jamieson2022nanobodiesidentifyan pages 4-8).  
Cys104 occupies the position equivalent to Tyr134 in TRIB1, introducing a solvent-accessible nucleophile within the pseudo-active site (jamieson2022nanobodiesidentifyan pages 15-19).  
Nanobody binding stabilises a face-to-face TRIB2 dimer that mimics the activated conformation observed for substrate-bound TRIB1 (jamieson2022nanobodiesidentifyan pages 12-15).

## Regulation

Ser83 phosphorylation by p70-S6K marks TRIB2 for ubiquitination and proteasomal degradation mediated by β-TRCP and Smurf1 (mayoralvaro2021thecriticalrole pages 4-5).  
The C-terminal DQLVPD motif recruits the E3 ligases COP1, TRIM21, β-TRCP and Smurf1, enabling ubiquitination of TRIB2 or bound substrates (mayoralvaro2021thecriticalrole pages 4-5).  
The C-tail can bind intramolecularly to the pseudokinase N-lobe, masking the COP1-binding degron; ligand or nanobody engagement displaces the tail, unmasking the degron (jamieson2022nanobodiesidentifyan pages 12-15).  
Transcription is activated by E2F1, TAL1, NOTCH1 and Smad3, and repressed by C/EBPα-p42 and E2A; miR-99b/let-7e/125a, miR-511, miR-1297, let-7, miR-206 and miR-140 reduce TRIB2 mRNA, whereas miR-505 and miR-155 increase it (mayoralvaro2021thecriticalrole pages 4-5).

## Function

Expression pattern: Highest basal expression in lymphoid lineages and hematopoietic stem/progenitor cells; aberrant over-expression in melanoma, lung, liver, colorectal, pancreatic and ovarian cancers (mayoralvaro2021thecriticalrole pages 7-8).  
MAPK scaffold: The ILDHPWF motif binds MEK1 and MKK7, modulating ERK/JNK signalling (mayoralvaro2021thecriticalrole pages 2-4).  
Myeloid transcription control: TRIB2 associates with C/EBPα and, together with COP1 or TRIM21, directs its poly-ubiquitination and degradation, affecting myeloid differentiation and promoting leukemogenesis (salome2015trib2andthe pages 1-5).  
PI3K–AKT axis: Direct interaction with AKT enhances Ser473 phosphorylation, suppresses FOXO transcription factors and contributes to drug resistance in melanoma and other solid tumours (link2015tribblesbreakingbad pages 2-3).  
Innate immunity: TRIB2 binds NF-κB p100 and attenuates TLR5-induced NF-κB activation (unknownauthors2014biochemicalanalysisof pages 69-71).

## Inhibitors

Electrophilic compounds that covalently modify Cys104 within the pseudo-active site have been reported to attenuate TRIB2 function (jamieson2022nanobodiesidentifyan pages 28-32).

## Other Comments

Over-expression or dysregulation of TRIB2 is linked to acute myeloid leukaemia, T-ALL, melanoma, and multiple solid tumours, where elevated levels correlate with poor clinical outcome (mayoralvaro2021thecriticalrole pages 7-8).

References

1. (eyers2017tribblesinthe pages 1-2): P. Eyers, Karen Keeshan, and N. Kannan. Tribbles in the 21st century: the evolving roles of tribbles pseudokinases in biology and disease. Trends in Cell Biology, 27:284-298, Apr 2017. URL: https://doi.org/10.1016/j.tcb.2016.11.002, doi:10.1016/j.tcb.2016.11.002. This article has 244 citations and is from a domain leading peer-reviewed journal.
2. (eyers2017tribblesinthe pages 2-4): P. Eyers, Karen Keeshan, and N. Kannan. Tribbles in the 21st century: the evolving roles of tribbles pseudokinases in biology and disease. Trends in Cell Biology, 27:284-298, Apr 2017. URL: https://doi.org/10.1016/j.tcb.2016.11.002, doi:10.1016/j.tcb.2016.11.002. This article has 244 citations and is from a domain leading peer-reviewed journal.
3. (jamieson2022nanobodiesidentifyan pages 12-15): Sam A Jamieson, Michael Pudjihartono, Christopher R Horne, Robert C Day, James M Murphy, and Peter D Mace. Nanobodies identify an activated state of the trib2 pseudokinase. BioRxiv, Apr 2022. URL: https://doi.org/10.1101/2022.04.29.489987, doi:10.1101/2022.04.29.489987. This article has 8 citations.
4. (jamieson2022nanobodiesidentifyan pages 28-32): Sam A Jamieson, Michael Pudjihartono, Christopher R Horne, Robert C Day, James M Murphy, and Peter D Mace. Nanobodies identify an activated state of the trib2 pseudokinase. BioRxiv, Apr 2022. URL: https://doi.org/10.1101/2022.04.29.489987, doi:10.1101/2022.04.29.489987. This article has 8 citations.
5. (jamieson2022nanobodiesidentifyan pages 4-8): Sam A Jamieson, Michael Pudjihartono, Christopher R Horne, Robert C Day, James M Murphy, and Peter D Mace. Nanobodies identify an activated state of the trib2 pseudokinase. BioRxiv, Apr 2022. URL: https://doi.org/10.1101/2022.04.29.489987, doi:10.1101/2022.04.29.489987. This article has 8 citations.
6. (link2015tribblesbreakingbad pages 2-3): Wolfgang Link. Tribbles breaking bad: trib2 suppresses foxo and acts as an oncogenic protein in melanoma. Biochemical Society Transactions, 43:1085-1088, Oct 2015. URL: https://doi.org/10.1042/bst20150102, doi:10.1042/bst20150102. This article has 22 citations and is from a peer-reviewed journal.
7. (lohan2013thefunctionallydiverse pages 1-2): Fiona Lohan and Karen Keeshan. The functionally diverse roles of tribbles. Biochemical Society Transactions, 41:1096-1100, Jul 2013. URL: https://doi.org/10.1042/bst20130105, doi:10.1042/bst20130105. This article has 62 citations and is from a peer-reviewed journal.
8. (mayoralvaro2021thecriticalrole pages 2-4): Víctor Mayoral-Varo, Lucía Jiménez, and W. Link. The critical role of trib2 in cancer and therapy resistance. Cancers, May 2021. URL: https://doi.org/10.3390/cancers13112701, doi:10.3390/cancers13112701. This article has 41 citations and is from a peer-reviewed journal.
9. (mayoralvaro2021thecriticalrole pages 4-5): Víctor Mayoral-Varo, Lucía Jiménez, and W. Link. The critical role of trib2 in cancer and therapy resistance. Cancers, May 2021. URL: https://doi.org/10.3390/cancers13112701, doi:10.3390/cancers13112701. This article has 41 citations and is from a peer-reviewed journal.
10. (mayoralvaro2021thecriticalrole pages 7-8): Víctor Mayoral-Varo, Lucía Jiménez, and W. Link. The critical role of trib2 in cancer and therapy resistance. Cancers, May 2021. URL: https://doi.org/10.3390/cancers13112701, doi:10.3390/cancers13112701. This article has 41 citations and is from a peer-reviewed journal.
11. (richmond2020pseudokinasesatribble‐edged pages 1-2): Laura Richmond and Karen Keeshan. Pseudokinases: a tribble‐edged sword. The FEBS Journal, 287:4170-4182, Oct 2020. URL: https://doi.org/10.1111/febs.15096, doi:10.1111/febs.15096. This article has 67 citations.
12. (salome2015trib2andthe pages 1-5): Mara Salomè, Joana Campos, and Karen Keeshan. Trib2 and the ubiquitin proteasome system in cancer. Biochemical Society Transactions, 43:1089-1094, Oct 2015. URL: https://doi.org/10.1042/bst20150103, doi:10.1042/bst20150103. This article has 29 citations and is from a peer-reviewed journal.
13. (unknownauthors2014biochemicalanalysisof pages 69-71): Biochemical Analysis of Human Cancer-Associated Pseudokinases
14. (jamieson2022nanobodiesidentifyan pages 15-19): Sam A Jamieson, Michael Pudjihartono, Christopher R Horne, Robert C Day, James M Murphy, and Peter D Mace. Nanobodies identify an activated state of the trib2 pseudokinase. BioRxiv, Apr 2022. URL: https://doi.org/10.1101/2022.04.29.489987, doi:10.1101/2022.04.29.489987. This article has 8 citations.