## Phylogeny

Orthologs are reported in vertebrates (Homo sapiens, Mus musculus, Danio rerio) and invertebrates such as Drosophila melanogaster and Caenorhabditis elegans; several non-mammalian homologs lack either the TBC or rhodanese domain, indicating lineage-specific truncation events (cagwin2025decodingtbckfrom pages 1-2).  
Amino-acid identity among mammalian TBCK sequences exceeds 90 %, underscoring strong evolutionary constraint (wu2021multiplefunctionsof pages 1-3).  
The conserved TBC domain places TBCK in the TBC1 domain-containing kinase family within the “Other” group of the human kinome as catalogued by kinome surveys following the Manning classification (cagwin2025decodingtbckfrom pages 19-19, cagwin2025decodingtbckfrom pages 18-19).

## Reaction Catalyzed

An ATP-dependent phosphorylation reaction has not been demonstrated; the N-terminal domain lacks the G-loop, VAIK, HRD and DFG motifs required for catalysis, supporting pseudokinase status (cagwin2025decodingtbckfrom pages 4-6, liu2013tbckinfluencescell pages 7-9).

## Cofactor Requirements

No requirement for divalent metal ions or other cofactors has been established; biochemical nucleotide-binding data are absent (cagwin2025decodingtbckfrom pages 2-4).

## Substrate Specificity

TBCK is not represented in the human serine/threonine kinase substrate atlas, and no consensus phosphorylation motif or physiological kinase substrates have been identified (cagwin2025decodingtbckfrom pages 19-19, cagwin2025decodingtbckfrom pages 17-18).

## Structure

Domain organisation: pseudokinase domain (residues 1-273) → low-complexity linker 1 (274-425) → TBC Rab-GAP domain (426-710) → low-complexity linker 2 (710-790) → rhodanese-like domain (790-891) (cagwin2025decodingtbckfrom pages 4-6).  
AlphaFold model AF-Q8TEA7-F1 predicts well-folded individual domains connected by flexible linkers, giving an elongated modular architecture (cagwin2025decodingtbckfrom pages 1-2, cagwin2025decodingtbckfrom pages 2-4).  
Pseudokinase domain: retains the bilobal kinase fold but catalytic Lys, HRD Asp and DFG Asp are replaced, generating a shallow nucleotide pocket incompatible with ATP binding (cagwin2025decodingtbckfrom pages 4-6).  
TBC domain: harbours the IX₂DX₂R “R-finger” (Arg511) and YXQ “Q-finger” arranged as in canonical Rab-GAPs; mutation of Arg511 (p.Arg511His) disrupts GAP activity in patient cells (chong2016recessiveinactivatingmutationsa pages 6-9).  
Rhodanese-like domain: conserves the DXR scaffold but lacks the catalytic cysteine, indicating a protein-interaction rather than enzymatic role (cagwin2025decodingtbckfrom pages 8-9).  
Cryo-EM of the FERRY complex (PMID 37267905) shows TBCK occupying a peripheral position while remaining unresolved at high resolution (cagwin2025decodingtbckfrom pages 17-17).  
TBCK is the only human TBC protein fused to a pseudokinase domain, combining predicted scaffolding and Rab-GAP modules in one polypeptide (cagwin2025decodingtbckfrom pages 4-6).

## Regulation

Reported post-translational modifications derived from large-scale proteomics:  
– Phosphorylation: Ser118, Tyr153, Thr169 (pseudokinase domain); Tyr732, Thr775, Thr782, Ser784 (linker 2) (cagwin2025decodingtbckfrom pages 4-6).  
– Ubiquitination: Lys271 (pseudokinase); Lys285, Lys343, Lys349 (linker 1); Lys450, Lys456, Lys461, Lys495, Lys706 (TBC); Lys881 (rhodanese) (cagwin2025decodingtbckfrom pages 6-8, cagwin2025decodingtbckfrom pages 8-9).  
– Acetylation: Lys450, Lys456, Lys461, Lys495, Lys706 (TBC) (cagwin2025decodingtbckfrom pages 6-8).  
– Arginine monomethylation: Arg503 (TBC) (cagwin2025decodingtbckfrom pages 6-8).  
Enzymes responsible for these modifications and their functional consequences have not been defined (cagwin2025decodingtbckfrom pages 6-8).

## Function

Expression and localisation: TBCK is cytosolic and enriched near the nucleus, centrosomes and the mitotic spindle in HEK293 and HeLa cells (cagwin2025decodingtbckfrom pages 9-10, wu2021multiplefunctionsof pages 3-4).  
Complex assembly: constitutes one of five subunits of the FERRY complex together with PPP1R21, CRYZL1, C12ORF4 and GATD1; the complex binds RAB5A-GTP, mRNAs and ribosomes to mediate early-endosomal mRNA transport (cagwin2025decodingtbckfrom pages 8-9, cagwin2025decodingtbckfrom pages 17-17).  
mTOR signalling: TBCK knock-down reduces transcription and protein levels of mTOR, Raptor, Rictor and mLST8, leading to diminished phosphorylation of 4E-BP1, p70 S6K and Akt-Ser473 (liu2013tbckinfluencescell pages 6-7, cagwin2025decodingtbckfrom pages 17-17).  
Actin cytoskeleton: depletion disrupts stress fibres and lowers F-actin intensity without affecting microtubules (liu2013tbckinfluencescell pages 6-7).  
Autophagy–lysosome–mitochondria axis: loss of TBCK produces autophagosome accumulation, lysosomal dysfunction, increased reactive oxygen species and impaired oxidative phosphorylation in neuronal models (angireddy2024anovelhuman pages 12-14).  
Interactome studies identify associations with centrosomal proteins, TRIM27, JIP4 and mitochondrial quality-control factors, suggesting additional roles in vesicle trafficking and mitophagy (floresmendez2025tbckdeficiencyleadsto pages 7-10).

## Other Comments

Disease association: biallelic loss-of-function variants cause TBCK syndrome (infantile hypotonia with psychomotor retardation type 3), characterised by developmental delay, brain atrophy, seizures and multi-organ involvement (durham2023tbcksyndromea pages 1-3, durham2023tbcksyndromea pages 3-4).  
Pathogenic mutations include the splice-site change NM\_033115:c.1708+1G>A and the missense p.Arg511His disrupting the TBC R-finger, both markedly reducing TBCK protein levels (cagwin2025decodingtbckfrom pages 1-2, chong2016recessiveinactivatingmutationsa pages 13-17).  
Somatic frameshift and missense mutations occur in colorectal adenocarcinoma and head-and-neck squamous carcinoma, implicating TBCK in tumorigenesis (liu2013tbckinfluencescell pages 6-7, wu2021multiplefunctionsof pages 4-5).

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