## Phylogeny

TBCK orthologues are present across vertebrates (e.g., Homo sapiens, Mus musculus, Danio rerio) and invertebrates (Drosophila melanogaster, Caenorhabditis elegans). Several non-mammalian homologues have lost either the TBC or rhodanese domain, suggesting lineage-specific truncations (Cagwin et al., 2025). Amino-acid identity among mammalian sequences exceeds 90 %, indicating strong evolutionary constraint (Wu & Lu, 2021). The conserved TBC domain groups TBCK with the TBC1 domain-containing kinase family in the “Other” branch of the human kinome (Cagwin et al., 2025).

## Reaction Catalyzed

No ATP-dependent phosphorylation reaction has been demonstrated. The N-terminal pseudokinase domain lacks the canonical G-loop, VAIK, HRD and DFG motifs required for catalysis, supporting classification as a pseudokinase (Cagwin et al., 2025; Liu et al., 2013).

## Cofactor Requirements

No divalent metal ions or other cofactors are known; biochemical nucleotide-binding data are lacking (Cagwin et al., 2025).

## Substrate Specificity

TBCK is absent from the human serine/threonine kinase substrate atlas, and no consensus phosphorylation motif or physiological substrates have been identified (Cagwin et al., 2025).

## Structure

Domain organisation: pseudokinase (1–273) → low-complexity linker-1 (274–425) → TBC Rab-GAP (426–710) → low-complexity linker-2 (711–790) → rhodanese-like (791–891) (Cagwin et al., 2025).  
AlphaFold model AF-Q8TEA7-F1 predicts well-folded individual domains joined by flexible linkers, producing an elongated architecture (Cagwin et al., 2025).  
• Pseudokinase domain: retains the bilobal kinase fold but key catalytic residues are replaced, creating a shallow pocket incompatible with ATP binding (Cagwin et al., 2025).  
• TBC domain: contains canonical IX₂DX₂R “R-finger” (Arg511) and YXQ “Q-finger”; mutation p.Arg511His abolishes Rab-GAP activity in patient cells (Chong et al., 2016).  
• Rhodanese-like domain: preserves the DXR scaffold but lacks the catalytic cysteine, implying a scaffolding role (Cagwin et al., 2025).  
Cryo-EM of the FERRY complex positions TBCK peripherally, but the protein remains unresolved at high resolution (Cagwin et al., 2025). TBCK is the sole human TBC protein fused to a pseudokinase domain.

## Regulation

High-throughput proteomics report multiple post-translational modifications (PTMs):  
– Phosphorylation: Ser118, Tyr153, Thr169, Tyr732, Thr775, Thr782, Ser784  
– Ubiquitination: Lys271, Lys285, Lys343, Lys349, Lys450, Lys456, Lys461, Lys495, Lys706, Lys881  
– Acetylation: Lys450, Lys456, Lys461, Lys495, Lys706  
– Arginine monomethylation: Arg503  
Enzymes responsible for these PTMs and their functional consequences are unknown (Cagwin et al., 2025).

## Function

Expression/localisation: cytosolic with enrichment around the nucleus, centrosomes and mitotic spindle in HEK293 and HeLa cells (Cagwin et al., 2025; Wu & Lu, 2021).  
Complex assembly: one of five subunits of the FERRY complex (with PPP1R21, CRYZL1, C12ORF4, GATD1); the complex binds RAB5A-GTP, mRNAs and ribosomes to mediate early-endosomal mRNA transport (Cagwin et al., 2025).  
Signalling: TBCK knock-down decreases transcription and protein levels of mTOR, Raptor, Rictor and mLST8, reducing phosphorylation of 4E-BP1, p70 S6K and Akt-Ser473 (Liu et al., 2013; Cagwin et al., 2025).  
Cytoskeleton: depletion disrupts stress fibres and lowers F-actin intensity without affecting microtubules (Liu et al., 2013).  
Autophagy–lysosome–mitochondria axis: loss of TBCK causes autophagosome accumulation, lysosomal dysfunction, elevated ROS and impaired oxidative phosphorylation in neuronal models (Angireddy et al., 2024).  
Interactome studies reveal associations with centrosomal proteins, TRIM27, JIP4 and mitochondrial quality-control factors, suggesting additional roles in vesicle trafficking and mitophagy (Flores-Mendez et al., 2025).

## Other Comments

Biallelic loss-of-function variants cause TBCK syndrome (infantile hypotonia with psychomotor retardation type 3) featuring developmental delay, brain atrophy, seizures and multi-organ involvement (Durham et al., 2023). Pathogenic alleles include splice variant c.1708+1G>A and missense p.Arg511His, both markedly reducing protein levels (Cagwin et al., 2025; Chong et al., 2016). Somatic frameshift and missense mutations are reported in colorectal adenocarcinoma and head-and-neck squamous carcinoma, implicating TBCK in tumorigenesis (Liu et al., 2013; Wu & Lu, 2021).

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