## Phylogeny

Orthologs have been identified in Homo sapiens, Mus musculus, Rattus norvegicus, Danio rerio, Drosophila melanogaster (Asator), and Caenorhabditis elegans (H05L14.1/dkf-2), reflecting conservation of the catalytic domain from invertebrates to vertebrates (taylor2019tautubulinkinases pages 4-5, liachko2014thetautubulin pages 3-5).  
Large-scale kinome phylogeny places TTBK1 within the Casein Kinase 1 (CK1) group, Tau-tubulin kinase (TTBK) family (manning2002theproteinkinase pages 3-3).  
The closest human paralogue is TTBK2, sharing 88 % identity and 96 % similarity across residues 23-280 of the kinase domain (bao2021mechanismsofregulation pages 1-2).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr/Tyr → ADP + protein-L-Ser/Thr/Tyr-phosphate (ikezu2014tautubulinkinase pages 3-5).

## Cofactor Requirements

Catalysis requires a divalent cation; crystal structures were solved with Mg²⁺ coordinating ATP/ADP in the active site (xue2013x‐raystructuralanalysis pages 1-2).

## Substrate Specificity

Direct cellular substrates include MAPT/tau (Ser198, Ser199, Ser202, Thr231, Ser396, Ser422, Tyr197), α/β-tubulin, TDP-43 (Ser409/Ser410), SV2A, Cep164, MAP1B and additional MAP family members (dillon2020acuteinhibitionof pages 2-4, bao2021mechanismsofregulation pages 12-13, bao2021mechanismsofregulation pages 1-2).  
A definitive TTBK1 consensus motif has not been resolved; the paralogous kinase TTBK2 prefers S/T-X-pY(+2) or primed CK1-type pS/pT-X-X-S/T motifs, but TTBK1 was not profiled in the kinome-wide motif atlas (johnson2023anatlasof pages 2-3, ikezu2014tautubulinkinase pages 2-3).

## Structure

Domain organisation  
• N-terminal kinase domain, residues 34-297, containing VAIK (Lys63), HRD (Asp164) and DFG (176-178) catalytic motifs (xue2013x‐raystructuralanalysis pages 2-4).  
• Central regulatory region (297-770) harbouring multiple autophosphorylation sites required for activity and localisation (bao2021mechanismsofregulation pages 13-14).  
• Unique poly-glutamate stretch, residues 733-771, responsible for anomalous SDS-PAGE mobility (nozal2019tautubulinkinase pages 1-7).  
• C-terminal region with SxIP and PEST motifs implicated in protein–protein interactions and turnover (kiefer2014thestructureof pages 1-2).

3-D structures  
Five high-resolution crystal structures of the kinase domain (PDB 4BTJ, 4BTK, 4BTM, 4NFN, 4NFM) reveal the canonical bilobed kinase fold with a properly aligned C-helix (Glu79), ordered activation segment including the APE motif, and intact regulatory/catalytic hydrophobic spines (kiefer2014thestructureof pages 1-2, xue2013x‐raystructuralanalysis pages 1-2).  
AlphaFold predicts the full-length architecture and positions the acidic insertions adjacent to the activation loop (bao2021mechanismsofregulation pages 5-7).

Unique features  
A flexible insertion N-terminal to the activation loop and the extended poly-glutamate tract are not present in other CK1 family members and may modulate substrate engagement (bao2021mechanismsofregulation pages 5-7).

## Regulation

Post-translational modifications  
• Autophosphorylation: thirteen sites identified—S320, T321, S322, T323, S324, T325, T344, S529, S540, S821, S942, S943, S1061 (bao2021mechanismsofregulation pages 8-10).  
‑ Phospho-silencing (13S→D) abolishes tau-S422 phosphorylation; phospho-mimetic (13S→A) reduces activity by ~65 % (bao2021mechanismsofregulation pages 8-10).  
• Trans-phosphorylation: TTBK1 phosphorylates TTBK2 in cells (bao2021mechanismsofregulation pages 13-14).  
• Proteolytic processing produces smaller fragments detected in neurodegenerative brain tissue (taylor2019tautubulinkinases pages 4-5).  
No ubiquitination events have been reported (bao2021mechanismsofregulation pages 13-14).  
Allosteric regulation has not been described.

## Function

Expression pattern  
TTBK1 mRNA and protein are highly enriched in adult human and mouse cerebral cortex, hippocampus and cerebellar granule layer; expression is negligible in peripheral tissues (bao2021mechanismsofregulation pages 5-7, nozal2019tautubulinkinase pages 1-7).

Molecular roles  
• Cytoskeletal control: interacts with MAPT, MAP1A/B, MAP2/6, MAP7D2 and MAPRE1, influencing microtubule plus-end dynamics (+TIP) (bao2021mechanismsofregulation pages 12-13).  
• Vesicular trafficking: associates with DVL1-3 and AAK1, linking to WNT-regulated endocytic sorting (bao2021mechanismsofregulation pages 12-13).  
• Tau regulation: phosphorylation decreases tau-microtubule affinity, impairs tubulin polymerisation and promotes tau aggregation (dillon2020acuteinhibitionof pages 2-4).  
• TDP-43 regulation: phosphorylation at Ser409/410 facilitates cytoplasmic inclusion formation (dillon2020acuteinhibitionof pages 2-4).

Upstream regulators have not been definitively identified; downstream effects converge on cytoskeletal organisation and synaptic function (bao2021mechanismsofregulation pages 12-13).

## Inhibitors

BIIB-TTBKi-284: ATP-competitive, IC₅₀ ≈ 15 nM (TTBK1) and 8 nM (TTBK2); inhibits 13/150 kinases >50 % at 3 µM (bao2021mechanismsofregulation pages 13-14).  
BIIB-TTBK1i: brain-penetrant probe; IC₅₀ ≈ 9.8 nM for tau-S422 reduction; 82 % in vivo target occupancy at 75 mg kg⁻¹ with high kinome selectivity (dillon2020acuteinhibitionof pages 8-9).  
AZ-1 and AZ-2: anilinoquinazoline derivatives; IC₅₀ = 4.4 µM (AZ-1) and 2.6 µM (AZ-2) against TTBK1; confer neuroprotection in phospho-TDP-43 cellular assays (baier2022ck2andprotein pages 10-13).

## Other Comments

Disease associations  
Elevated TTBK1 expression and kinase activity correlate with Alzheimer’s disease, frontotemporal dementia, amyotrophic lateral sclerosis, chronic traumatic encephalopathy and Down’s syndrome (nozal2019tautubulinkinase pages 24-25).  
Genome-wide association studies identify TTBK1 SNPs modulating Alzheimer’s disease risk, but specific pathogenic missense or truncating variants such as p.R141\* or p.M677Kfs\*15 have not been reported (nozal2019tautubulinkinase pages 11-14).

Therapeutic relevance  
Selective inhibition of TTBK1 lowers pathological tau and TDP-43 phosphorylation in preclinical models, highlighting the kinase as a potential target for modifying neurodegenerative disease progression (dillon2020acuteinhibitionof pages 2-4, bao2021mechanismsofregulation pages 13-14).

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