1. Phylogeny  
   Dual specificity protein kinase TTK, also referred to as Mps1, is a member of the Mps1 family of protein kinases that is highly conserved from yeast to humans, with orthologs identified in Saccharomyces cerevisiae, Schizosaccharomyces pombe, Drosophila, and vertebrate species, thus reflecting its origin in the last eukaryotic common ancestor (liu2012themps1family pages 1-2). TTK is phylogenetically grouped with kinases that regulate the spindle assembly checkpoint (SAC) and is evolutionarily related to other checkpoint proteins such as Bub1 and BubR1, which share structural and functional features necessary for mitotic fidelity (pachis2018leaderofthe pages 1-2). Comparative studies have shown that the domain architecture of TTK is maintained across species, with its catalytic core and regulatory regions displaying high conservation among eukaryotes (dou2011quantitativemassspectrometry pages 1-2). As a member of the human kinome, TTK is placed in a subgroup of dual specificity kinases that uniquely phosphorylate serine/threonine as well as tyrosine residues, and this feature underscores its evolutionary divergence from classical serine/threonine kinases (liu2012themps1family pages 1-2). The conservation of TTK’s functional motifs and overall domain organization supports its inclusion among a core set of mitotic regulators that originated early in eukaryotic evolution (ashraf2022combined3dqsarmolecular pages 1-2).
2. Reaction Catalyzed  
   TTK catalyzes the transfer of the γ-phosphate group from ATP to the hydroxyl group of serine, threonine, or tyrosine residues on substrate proteins, resulting in the formation of ADP and a phosphorylated protein product (ashraf2022combined3dqsarmolecular pages 1-2). This phosphorylation reaction is central to TTK’s role in modulating the function of key mitotic proteins, thereby ensuring the proper timing of mitosis and maintenance of genomic stability (dou2011quantitativemassspectrometry pages 1-2).
3. Cofactor Requirements  
   The enzymatic activity of TTK is dependent on the presence of divalent cations such as Mg²⁺, which serve as essential cofactors by stabilizing the binding of ATP within the kinase’s active site and facilitating catalysis (liu2012themps1family pages 1-2).
4. Substrate Specificity  
   TTK is characterized as a dual specificity kinase capable of phosphorylating both serine/threonine and tyrosine residues, a feature that underpins its broad substrate repertoire (dou2011quantitativemassspectrometry pages 1-2). Its substrates include a variety of proteins integral to the spindle assembly checkpoint; for example, TTK phosphorylates MAD1L1, a modification that promotes checkpoint complex assembly and delays anaphase onset (ashraf2022combined3dqsarmolecular pages 18-19). In addition, TTK phosphorylates CDCA8 (Borealin) which in turn enhances Aurora B kinase activity at the kinetochore, thereby contributing to the correction of improper kinetochore-microtubule attachments (ashraf2022combined3dqsarmolecular pages 18-19). The kinase also targets SKA3 at serine residue 34, leading to the dissociation of the SKA complex from microtubules and modulation of kinetochore attachment dynamics (ashraf2022combined3dqsarmolecular pages 1-2). Moreover, TTK phosphorylates other checkpoint proteins including KNL1 and KNTC1 and is known to autophosphorylate, which may participate in a feedback loop regulating its own activity (bayliss2012onthemolecular pages 5-6).
5. Structure  
   TTK is a large protein consisting of 857 amino acids and is organized into several distinct regions that together mediate its catalytic and regulatory functions. Its central kinase domain exhibits a typical dual-lobed structure, with a smaller N-terminal lobe composed primarily of six β-sheets and one α-helix, and a larger C-terminal lobe that contains multiple α-helices, including the activation and catalytic loops critical for substrate recognition and phosphoryl transfer (ashraf2022combined3dqsarmolecular pages 1-2). In addition to the kinase domain, the N-terminal region of TTK contains tetratricopeptide repeat (TPR) motifs that are essential for kinetochore localization and protein–protein interactions during mitosis (pachis2018leaderofthe pages 2-3). The kinase domain features key structural elements such as the glycine-rich loop, the conserved catalytic loop, an activation loop that undergoes autophosphorylation, and a C-helix that participates in aligning catalytic residues; these elements are critical for TTK’s enzymatic activity (liu2012themps1family pages 9-10). A unique aspect of TTK’s structure is a cysteine residue (Cys604) located in the hinge region of the kinase domain, which creates an enlarged pocket and has been exploited for the development of selective inhibitors (riggs2019designandoptimization pages 9-10). Crystallographic studies have often captured the TTK kinase domain in an inactive conformation, even when autophosphorylated, indicating that the active conformation may be transient or dynamic in nature (liu2012themps1family pages 9-10, serafim2022developmentofthe pages 9-12).
6. Regulation  
   The regulation of TTK activity is predominantly achieved through post-translational modifications, most notably autophosphorylation within its activation loop. Phosphorylation events at key residues such as Thr676 and Thr686 are critical for the conformational switch from an inactive state to a fully active kinase conformation (liu2012themps1family pages 15-16, yang2009structuralandmechanistic pages 9-10). In addition to autophosphorylation, TTK is subject to regulation by upstream kinases such as Aurora B, which modulate its kinetochore localization and functional activity during mitosis (pachis2018leaderofthe pages 7-8). TTK is recruited to unattached kinetochores early in mitosis, where its activation is essential for the assembly of the spindle assembly checkpoint complex, thereby preventing premature anaphase onset (ashraf2022combined3dqsarmolecular pages 1-2, bayliss2012onthemolecular pages 5-6). Moreover, TTK levels and activity are regulated by the cell cycle–dependent ubiquitination and degradation mediated by the anaphase-promoting complex/cyclosome (APC/C), which ensures that TTK activity is limited to appropriate phases of mitosis (liu2012themps1family pages 21-22). These multiple layers of regulation ensure strict spatial and temporal control over TTK’s kinase activity, which is vital for maintaining genomic stability during cell division (pachis2018leaderofthe pages 8-8).
7. Function  
   TTK is a key effector in the spindle assembly checkpoint (SAC), a critical safeguard mechanism that monitors the attachment of chromosomes to the mitotic spindle and prevents the onset of anaphase until every chromosome is correctly bioriented. By phosphorylating MAD1L1, TTK facilitates the generation and maintenance of the mitotic checkpoint complex, thereby delaying cell cycle progression until proper kinetochore–microtubule attachments are achieved (ashraf2022combined3dqsarmolecular pages 18-19). In addition, the phosphorylation of CDCA8 (Borealin) by TTK enhances the activity of Aurora B kinase at the kinetochore, which is necessary for the correction of erroneous microtubule attachments and proper chromosome congression (ashraf2022combined3dqsarmolecular pages 18-19). Furthermore, TTK phosphorylates SKA3 at serine 34, a modification that leads to the dissociation of the SKA complex from microtubules and plays a role in the destabilization and subsequent correction of kinetochore attachments (ashraf2022combined3dqsarmolecular pages 1-2). The kinase also targets other proteins such as KNL1 and KNTC1 and is capable of autophosphorylation, which may serve to fine-tune its activity during different phases of mitosis (bayliss2012onthemolecular pages 5-6, dou2011quantitativemassspectrometry pages 8-8). Owing to these fundamental roles, TTK is essential for the maintenance of genomic integrity, and its dysregulation has been linked to chromosomal instability in a range of cancers including triple‐negative breast cancer, pancreatic ductal adenocarcinoma, lung cancer, and endometrial cancer (maire2013ttkhmps1isan pages 1-2, tsai2020upregulationofthrtyr pages 18-20, du2024upregulationofttk pages 12-13).
8. Other Comments  
   TTK has emerged as a prominent target in cancer therapy due to its central role in ensuring accurate chromosome segregation and its frequent overexpression in a variety of aggressive tumors. Several small-molecule inhibitors have been developed to target TTK; among these are compounds such as CCT251455, CFI-402257, BOS172722, S81694, BAY1161909, and BAY1217389, which exhibit low nanomolar potency and have been validated in preclinical studies (ashraf2022combined3dqsarmolecular pages 1-2). In structure-guided drug discovery efforts, inhibitors have been optimized by exploiting unique features of the TTK kinase domain, including the rare cysteine residue in the hinge region (Cys604), which allows for the development of covalent inhibitors such as RMS-07 that prolong target residence time (riggs2019designandoptimization pages 9-10, serafim2022developmentofthe pages 9-12, uitdehaag2017targetresidencetimeguided pages 19-20). Clinically, TTK overexpression correlates with poor prognosis in cancers such as endometrial cancer and lung cancer, and its inhibition has been shown to impair cancer cell proliferation by inducing fatal chromosomal instability (du2024upregulationofttk pages 12-13, tsai2020upregulationofthrtyr pages 18-20, stratford2017geneticandpharmacological pages 7-9). In addition, TTK has been implicated in regulating the subcellular localization of oncogenic proteins, as demonstrated by its role in phosphorylating c-Abl in a manner that affects its distribution between the nucleus and cytoplasm (nihira2008ttkmps1controlsnuclear pages 1-2). Such multifaceted roles continue to fuel the interest in developing highly selective TTK inhibitors as potential therapeutics for cancer treatment (stratford2017geneticandpharmacological pages 7-9).
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