1. Phylogeny  
   STK36, also known as Fused homolog, is a serine/threonine protein kinase that is evolutionarily conserved across eukaryotes. In mammals, it is the human ortholog of the Drosophila Fused (Fu) kinase and is present in species ranging from unicellular flagellates to higher vertebrates, which underscores its ancient evolutionary origin and importance in developmental signaling pathways (edelbusch2017mutationofserinethreonine pages 1-5, krupa2002therepertoireof pages 12-13). Within the kinome, STK36 is classified among serine/threonine kinases with a specialized role in the Sonic Hedgehog (Shh) pathway, where it shares phylogenetic attributes with other kinases involved in developmental processes and ciliogenesis. Its evolutionary trajectory is marked by the conservation of the catalytic kinase domain along with divergence in its regulatory C-terminal regions, reflecting functional adaptations that have occurred after the gene duplication events characteristic of the metazoan lineage (edelbusch2017mutationofserinethreonine pages 1-5).
2. Reaction Catalyzed  
   STK36 catalyzes the phosphorylation reaction typical of serine/threonine protein kinases. The chemical reaction it mediates can be described as follows:  
   ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (goldsmith2007substrateanddocking pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of STK36 is dependent on the presence of divalent metal ions, with Mg²⁺ being the primary cofactor required for efficient ATP binding and phosphate transfer to the substrate (goldsmith2007substrateanddocking pages 1-2).
4. Substrate Specificity  
   Although a consensus substrate motif for STK36 has not been formally defined in the literature, functional studies indicate that STK36 is involved in the regulation of key transcription factors within the Shh signaling pathway. In particular, STK36 modulates the activity of the GLI family of transcription factors (GLI1, GLI2, and GLI3) by counteracting the inhibitory effects of SUFU and promoting their nuclear localization (edelbusch2017mutationofserinethreonine pages 1-5). While kinases such as PKA, CK1, and GSK3β are known to phosphorylate GLI proteins at specific consensus sequences, STK36 appears to regulate GLI proteins in a manner that does not strictly depend on its kinase activity; for example, GLI2 requires an additional function provided by STK36 to become transcriptionally active even when STK36 is catalytically inactive (edelbusch2017mutationofserinethreonine pages 1-5, goldsmith2007substrateanddocking pages 7-9).
5. Structure  
   STK36 is a relatively large protein comprising 1315 amino acids. The protein organization includes an N-terminal kinase catalytic domain that exhibits the canonical bilobal structure typical of serine/threonine kinases, with a smaller N-terminal lobe largely consisting of β-sheets and a larger C-terminal lobe dominated by α-helices (goldsmith2007substrateanddocking pages 1-2). This kinase domain harbors key motifs including the ATP-binding site, the catalytic loop, and the activation segment with its associated regulatory phosphorylation sites. The C-terminal portion of STK36 is considerably longer and more divergent in sequence; although it lacks well-defined folded domains such as a MIT domain—which is present in related kinases like ULK3—this region is thought to mediate protein–protein interactions that are crucial for its regulatory functions (edelbusch2017mutationofserinethreonine pages 1-5). Despite the fact that crystallographic data for STK36 are not available, predicted structural models (e.g., those from AlphaFold) suggest that the overall architecture of its kinase domain is consistent with that observed for other serine/threonine kinases, including the presence of a hydrophobic spine and a C-helix that contribute to catalytic activity and conformational regulation (goldsmith2007substrateanddocking pages 1-2, wang2019serinethreonineproteinkinase pages 3-5).
6. Regulation  
   Regulation of STK36 involves a combination of posttranslational modifications and protein–protein interactions that modulate its function within the Shh signaling cascade. Notably, STK36 is known to regulate GLI transcription factors by opposing the inhibitory activity of SUFU and by promoting their nuclear localization (edelbusch2017mutationofserinethreonine pages 1-5). Functional analyses have demonstrated that the ability of STK36 to enhance GLI2-mediated transcription does not require an active kinase catalytic site, which suggests that non-catalytic functions such as scaffolding or stabilization of GLI proteins and associated complexes are critical for its role in signal transduction (edelbusch2017mutationofserinethreonine pages 1-5). Although specific phosphorylation sites on STK36 itself have not been comprehensively characterized in the available literature, regulatory mechanisms likely include conformational shifts triggered by autophosphorylation or allosteric changes induced by binding partners, which in turn influence its localization to cilia and interaction with other regulatory proteins (goldsmith2007substrateanddocking pages 6-7, flax2024illuminationofunderstudied pages 6-7).
7. Function  
   STK36 plays a pivotal role in the Sonic Hedgehog (Shh) signaling pathway by modulating the activity of GLI transcription factors. It acts to counterbalance the inhibitory effects of SUFU, thereby promoting the nuclear localization and transcriptional activity of GLI proteins—specifically enabling GLI2 to drive target gene expression even in the absence of STK36 kinase activity (edelbusch2017mutationofserinethreonine pages 1-5). In addition to its role in Shh signal transduction, STK36 is essential for postnatal development, most notably through its involvement in the construction of the central pair apparatus of motile cilia. Defects in STK36 have been linked to primary ciliary dyskinesia (PCD) with central pair defects, and its function in maintaining cerebrospinal fluid homeostasis may contribute to proper neural development (edelbusch2017mutationofserinethreonine pages 1-5, zhou2023ulk4promotesshh pages 19-20). The expression of STK36 is observed in tissues known for active Hedgehog signaling, including specific regions of the brain, respiratory epithelium, and testicular tissue, suggesting that its activity is closely tied to developmental and homeostatic processes that depend on ciliary function (edelbusch2017mutationofserinethreonine pages 1-5, park2011globalanalysisof pages 4-5).
8. Other Comments  
   No selective inhibitors for STK36 have been reported in the literature reviewed, and its substrate specificity remains incompletely defined relative to other kinases that target the GLI transcription factors. Mutations in STK36 have been associated with primary ciliary dyskinesia, underlying its clinical relevance in ciliopathies (edelbusch2017mutationofserinethreonine pages 1-5). Given its dual role in regulating GLI activity through both kinase-dependent and kinase-independent mechanisms, STK36 represents a potential target for genetic screening in patients with ciliary dysfunction and developmental anomalies. In addition, its involvement in Shh signaling and ciliary homeostasis suggests that further characterization of STK36 and its regulatory complexes may provide insight into therapeutic strategies for conditions associated with aberrant Shh pathway activation (edelbusch2017mutationofserinethreonine pages 1-5, zhou2023ulk4promotesshh pages 19-20).
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