## Phylogeny

STK36 is the mammalian homolog of Drosophila Fused (Fu) and is a highly conserved kinase with orthologs found across diverse organisms including plants, flagellated unicellular eukaryotes, *Chlamydomonas reinhardtii*, Drosophila, zebrafish, and planarian (edelbusch2017mutationofserinethreonine pages 1-5, edelbusch2017mutationofserinethreonine pages 5-8, zhou2023ulk4promotesshh pages 1-5). The human STK36 protein shares 66% sequence identity and 83% similarity with its ortholog in *Chlamydomonas reinhardtii* (edelbusch2017mutationofserinethreonine pages 1-5). According to the kinome classification by Manning et al., STK36 is assigned to the ‘Other’ group and is related to the ‘Fused’ subfamily of kinases (edelbusch2017mutationofserinethreonine pages 12-16, park2011globalanalysisof pages 3-4).

## Reaction Catalyzed

I cannot answer. The provided context does not contain the specific chemical reaction catalyzed by STK36, only general descriptions of its function as a serine/threonine kinase that transfers a phosphate group from ATP to substrates (johnson2023anatlasof pages 4-5, zhou2023ulk4promotesshh pages 29-32).

## Cofactor Requirements

The catalytic activity of STK36 requires ATP and Mg2+ as cofactors (edelbusch2017mutationofserinethreonine pages 12-16, johnson2023anatlasof pages 4-5, zhou2023ulk4promotesshh pages 27-29).

## Substrate Specificity

I cannot answer. The provided context repeatedly states that the consensus substrate phosphorylation motif for STK36 is detailed in the supplementary materials of the Johnson et al., 2023 publication, but the content of these supplementary materials, which would contain the specific amino acid preferences at each position, is not included in the context (johnson2023anatlasof pages 1-2, johnson2023anatlasof pages 6-7, johnson2023anatlasof pages 5-6). The context only provides a general description that STK36 may prefer proline-directed substrate motifs (johnson2023anatlasof pages 4-5).

## Structure

STK36 consists of a highly conserved N-terminal kinase domain (amino acids 1-260) and a less conserved C-terminal regulatory region (unknownauthors2014dierolleder pages 16-19, zhou2023ulk4promotesshh pages 9-12). The N-terminal kinase domain is responsible for binding both the pseudokinase ULK4 and the transcription factor GLI2 (zhou2023ulk4promotesshh pages 32-36). AlphaFold models predict a typical bilobal kinase fold containing key catalytic residues essential for ATP binding and phosphotransferase activity (edelbusch2017mutationofserinethreonine pages 12-16, johnson2023anatlasof pages 4-5). The kinase domain contains a conserved activation loop with key serine/threonine phosphorylation sites, including threonine 158 and serine 159 (T158/S159), which are important for kinase activity (edelbusch2017mutationofserinethreonine pages 5-8, zhou2023ulk4promotesshh pages 29-32, zhou2023ulk4promotesshh pages 15-19, zhou2023ulk4promotesshh pages 9-12).

## Regulation

STK36 activity is regulated by post-translational phosphorylation and protein-protein interactions (edelbusch2017mutationofserinethreonine pages 12-16, johnson2023anatlasof pages 4-5). Upon Sonic Hedgehog (Shh) pathway stimulation, STK36 undergoes kinase-activity-dependent trans-autophosphorylation on its activation loop at residues T158 and S159 (edelbusch2017mutationofserinethreonine pages 5-8, zhou2023ulk4promotesshh pages 15-19, zhou2023ulk4promotesshh pages 32-36, zhou2023ulk4promotesshh pages 9-12). Phosphorylation at nearby residues S151 and T154 also modulates its kinase activity (zhou2023ulk4promotesshh pages 9-12). STK36 forms a constitutive complex with the pseudokinase ULK4 and the transcription factor GLI2 (zhou2023ulk4promotesshh pages 15-19). ULK4 acts as a scaffold, facilitating GLI2 phosphorylation without directly altering STK36’s intrinsic kinase activity (zhou2023ulk4promotesshh pages 1-5, zhou2023ulk4promotesshh pages 15-19, zhou2023ulk4promotesshh pages 9-12). The accumulation of both STK36 and ULK4 at the ciliary tip is mutually dependent; STK36-mediated phosphorylation of ULK4 at Thr1021 and Thr1023 controls ULK4’s ciliary localization (zhou2023ulk4promotesshh pages 1-5, zhou2023ulk4promotesshh pages 12-15).

## Function

STK36 is highly expressed in motile ciliated tissues including respiratory epithelium, brain ependymal lining, oviduct, and testis, as well as in the brain, kidney, and pancreas (edelbusch2017mutationofserinethreonine pages 5-8, unknownauthors2014dierolleder pages 16-19). In the Sonic Hedgehog (Shh) signaling pathway, STK36 localizes to the tip of primary cilia, where it phosphorylates the transcription factor GLI2 at sites including S230 and S232, promoting GLI2 activation (zhou2023ulk4promotesshh pages 1-5, zhou2023ulk4promotesshh pages 32-36, zhou2023ulk4promotesshh pages 5-9). Its interacting partners include SUFU, GLI proteins, its scaffolding partner ULK4, central pair proteins SPAG16 and PCDP1, and the kinesin KIF27 (edelbusch2017mutationofserinethreonine pages 12-16, edelbusch2017mutationofserinethreonine pages 5-8, zhou2023ulk4promotesshh pages 29-32). STK36 is essential for ciliogenesis, where it localizes to the ciliary axoneme, likely between the radial spokes and the central pair (CP), and is required for proper CP construction and orientation of motile cilia (edelbusch2017mutationofserinethreonine pages 12-16, edelbusch2017mutationofserinethreonine pages 5-8, zhou2023ulk4promotesshh pages 29-32). In mice, STK36 is not required for Shh signaling, possibly due to functional redundancy with the kinase ULK3 (edelbusch2017mutationofserinethreonine pages 5-8, zhou2023ulk4promotesshh pages 15-19).

## Other Comments

Homozygous loss-of-function mutations in the *STK36* gene cause primary ciliary dyskinesia (PCD), a ciliopathy characterized by impaired mucociliary clearance and defects in the central pair of motile cilia, but typically without laterality defects (edelbusch2017mutationofserinethreonine pages 1-5, edelbusch2017mutationofserinethreonine pages 12-16, edelbusch2017mutationofserinethreonine pages 5-8). A homozygous frameshift mutation results in the loss of STK36 protein and disorganized orientation of the basal foot and central pair (edelbusch2017mutationofserinethreonine pages 5-8). STK36 disruption is also implicated in congenital hydrocephalus in mouse models and malignancies such as pancreatic adenocarcinoma and melanoma (zhou2023ulk4promotesshh pages 29-32, zhou2023ulk4promotesshh pages 27-29, unknownauthors2014dierolleder pages 16-19).

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