Protein/Gene: Dual serine/threonine and tyrosine protein kinase  
HGNC symbol: DSTYK UniProt: Q6XUX3  
Alternative names: Dusty protein kinase; Receptor-interacting serine/threonine-protein kinase 5 (RIP5/RIPK5); Sugen kinase 496; SGK496; KIAA0472 (peng2006dustyproteinkinases pages 1-2)

## Phylogeny

Single-copy kinase present in Homo sapiens, Mus musculus, Rattus norvegicus, Gallus gallus and Danio rerio, indicating broad conservation across vertebrates (peng2006dustyproteinkinases pages 1-2, unknownauthors2014dstykkinasedomain pages 7-7, sun2020dstykmutationleads pages 3-4).  
Kinase-domain homology assigns DSTYK to the receptor-interacting protein kinase (RIPK) family within the tyrosine kinase-like (TKL) branch of the human kinome (dong2025dstykphosphorylatessting pages 1-2).

## Reaction Catalyzed

Protein-L-Ser/Thr/Tyr + ATP ⇌ Protein-L-Ser/Thr/Tyr-phosphate + ADP + H⁺ (peng2006dustyproteinkinases pages 1-2).

## Cofactor Requirements

No divalent metal ion requirement has been reported in available experimental literature (dong2025dstykphosphorylatessting pages 2-3).

## Substrate Specificity

Direct, site-specific phosphorylation of STING at Ser366 (dong2025dstykphosphorylatessting pages 5-7).  
Phosphorylates β-catenin at unidentified residues in vitro (zhong2021lossofdstyk pages 4-7).  
A global consensus phosphorylation motif has not been defined.

## Structure

Domain organisation: two N-terminal non-catalytic regions (NCR1 and NCR2) enriched in cysteines and docking motifs, followed by a divergent eukaryotic protein kinase catalytic domain spanning residues 652-906 (peng2006dustyproteinkinases pages 1-2, sun2020dstykmutationleads pages 3-4).  
No crystallographic structures are available; AlphaFold or comparable models were not reported in current sources (dong2025dstykphosphorylatessting pages 2-3).  
Classical catalytic motifs (VAIK, HRD, DFG) are inferred by homology but have not been experimentally resolved.  
Kinase-dead mutants (K681A, D777A) retain STING binding and endosomal localisation, indicating that catalytic activity is dispensable for docking yet essential for phosphorylation (dong2025dstykphosphorylatessting pages 5-7).

## Regulation

TBK1-mediated phosphorylation of DSTYK enhances its capacity to phosphorylate STING after the latter reaches late endosomes (dong2025dstykphosphorylatessting pages 1-2).  
Electrophoretic mobility shifts of endogenous DSTYK suggest additional, unmapped post-translational modifications (unknownauthors2014dstykkinasedomain pages 5-7).  
Subcellular localisation: constitutively associates with Rab7/LAMP1-positive late endosomes; localisation is independent of kinase activity (dong2025dstykphosphorylatessting pages 5-7).  
Allosteric control: physical interaction with STING is maintained in kinase-inactive mutants, separating binding from catalytic activation (dong2025dstykphosphorylatessting pages 5-7).

## Function

Expression: high in innate immune cells (NK cells, dendritic cells, macrophages, neutrophils) and in multiple human lines including HEK293, HeLa, THP-1, A549, HT1080 and Hep-G2 (dong2025dstykphosphorylatessting pages 16-24).  
Innate immunity: at late endosomes DSTYK phosphorylates STING-Ser366, facilitating downstream phosphorylation of TBK1, IRF3, NF-κB p65 and IκBα, thereby driving IFNB, ISG and pro-inflammatory cytokine expression during DNA-virus infection (dong2025dstykphosphorylatessting pages 2-3, dong2025dstykphosphorylatessting pages 16-24).  
Cell death: over-expression triggers both caspase-dependent and caspase-independent death pathways (dong2025dstykphosphorylatessting pages 1-2).  
Wnt signalling and metabolism: phosphorylates β-catenin, lowers β-catenin accumulation and represses Axin2, c-Myc, cyclin D1 and LDHA, thereby limiting lung adenocarcinoma growth and stemness (zhong2021lossofdstyk pages 4-7).  
ERK pathway: a somatic Met296Ile mutation augments ERK1/2 activity and enhances invasiveness in solitary fibrous tumour/hemangiopericytoma (tang2019adstykmutation pages 4-6).

## Other Comments

Disease associations:  
• Heterozygous splice-site and missense variants cause autosomal dominant congenital anomalies of the kidney and urinary tract (CAKUT) (sannacherchi2013mutationsindstyk pages 4-5).  
• Missense variant c.271C>A (Leu91Met) linked to hereditary spastic paraparesis with lower urinary-tract dysfunction (vidic2021exomesequencingimplicates pages 2-4).  
• Loss-of-function alleles in zebrafish generate scoliosis-like vertebral malformations via mTORC1/TFEB dysregulation (sun2020dstykmutationleads pages 3-4).  
• Kinase-domain ablation in mice impairs spatial learning and memory without gross neurodevelopmental defects (unknownauthors2014dstykkinasedomain pages 5-7).  
• Cancer: Met296Ile somatic mutation drives intraspinal dissemination of solitary fibrous tumour/hemangiopericytoma (tang2019adstykmutation pages 4-6); reduced expression suppresses lung adenocarcinoma progression via β-catenin regulation (zhong2021lossofdstyk pages 4-7).

No specific small-molecule or biologic inhibitors have been described in the cited literature.

References

1. (dong2025dstykphosphorylatessting pages 2-3): Hao Dong, Heng Zhang, Pu Song, Yuan Hu, and Danying Chen. Dstyk phosphorylates sting at late endosomes to promote sting signaling. EMBO Reports, 26:1620-1646, Feb 2025. URL: https://doi.org/10.1038/s44319-025-00394-9, doi:10.1038/s44319-025-00394-9. This article has 0 citations and is from a highest quality peer-reviewed journal.
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