## Phylogeny

• STK32C (YANK3) is one of three paralogous kinases in the STK32 (YANK) subfamily together with STK32A and STK32B (sorrell2020stk32aisa pages 1-5).  
• Orthologs are restricted to bony vertebrates, indicating a recent evolutionary origin within vertebrates (sorrell2020stk32aisa pages 1-5).  
• The subfamily branches adjacent to Aurora kinases inside the AGC group and retains the complete C-terminal AGC extension (sorrell2020stk32aisa pages 5-7).  
• Kinome-wide substrate-motif clustering places STK32C in an acidophilic cluster of the human Ser/Thr kinome (johnson2023anatlasof pages 12-18).

## Reaction Catalyzed

ATP + protein L-serine/L-threonine/L-tyrosine ⇌ ADP + protein O-phospho-L-serine/O-phospho-L-threonine/O-phospho-L-tyrosine (sorrell2020stk32aisa pages 1-5).

## Cofactor Requirements

• Catalytic activity depends on divalent cations; manganese (Mn²⁺) supports higher activity than magnesium (Mg²⁺) in in-vitro assays of the STK32 family (sorrell2020stk32aisa pages 5-7).

## Substrate Specificity

• Peptide-library profiling categorises STK32C as acidophilic, favouring Asp/Glu residues flanking the phosphorylation site (johnson2023anatlasof pages 12-18).  
• The same profiling shows tolerance for pre-phosphorylated residues at positions −3 and +2 relative to the acceptor Ser/Thr (johnson2023anatlasof pages 2-3).

## Structure

• The protein comprises a bilobal kinase domain followed by an AGC-type C-terminal tail containing a turn motif and an atypical F-X-X-F-N-R hydrophobic motif in which the canonical phospho-Ser/Thr is replaced by Asn (sorrell2020stk32aisa pages 5-7).  
• A conserved “HF motif helix” spans the N-lobe–C-tail interface (sorrell2020stk32aisa pages 5-7).  
• Key catalytic motifs (VAIK, HRD, APE, and a DFN variant of DFG) are present (sorrell2020stk32aisa pages 5-7).  
• A homology model based on PDB 4FR4 illustrates a positively charged substrate groove compatible with acidic substrates (johnson2023anatlasof pages 12-18).  
• Several human isoforms lack the glycine-rich loop, a modification predicted to limit ATP binding (sorrell2020stk32aisa pages 5-7).  
• The ATP-binding site contains a small valine gatekeeper that enlarges the back pocket (sorrell2020stk32aisa pages 15-18).

## Regulation

• No experimentally verified post-translational modifications are reported.  
• Multiple putative phosphorylation sites occur within a Pro/Ala/Arg/Ser-rich N-terminal extension (~67 aa) (sorrell2020stk32aisa pages 5-7).  
• The hydrophobic-motif phospho-acceptor is absent (Ser/Thr → Asn), so regulation does not rely on this canonical AGC phosphorylation event (sorrell2020stk32aisa pages 5-7).

## Function

• Protein expression is ubiquitous across surveyed human tissues (sorrell2020stk32aisa pages 1-5).  
• Immunofluorescence under high ectopic expression shows primarily cytosolic localisation (sorrell2020stk32aisa pages 39-43).  
• No experimentally confirmed upstream kinases, downstream substrates, or signalling pathways are available in the cited literature (johnson2023anatlasof pages 12-18).

## Inhibitors

• Family-wide binding studies revealed interaction with Staurosporine, Ceritinib and the analogue-sensitive probe 1NM-PP1 (sorrell2020stk32aisa pages 1-5, sorrell2020stk32aisa pages 12-15).  
• The enlarged back pocket generated by the valine gatekeeper permits binding of inhibitors such as PP-121 (sorrell2020stk32aisa pages 15-18).

## Other Comments

• Differential methylation of the STK32C locus is associated with adolescent depression and with psychiatric-disorder risk in Down syndrome (sorrell2020stk32aisa pages 1-5).  
• Chemoproteomic screens classify STK32C as a potential anti-target because broad inhibitor engagement correlates with cytotoxicity (sorrell2020stk32aisa pages 1-5).

References

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