## Phylogeny

NUAK2 (SNARK; Omphalocele kinase 2) belongs to the NUAK sub-family of AMP-activated protein kinase–related kinases (ARKs) within the Ca²⁺/calmodulin-regulated (CAMK) branch of the human kinome, and is most closely related to NUAK1 (ARK5) (banerjee2014characterizationofwz4003 pages 1-2, vis2021nuak1andnuak2 pages 5-7).  
Orthologs are documented in Mus musculus (Nuak2 isoforms A/B), Rattus norvegicus (Snark), Danio rerio, Drosophila melanogaster, and Caenorhabditis elegans (unc-82), with conservation extending to yeast SNF1 as an out-group of the ARK lineage (minchenko2012snf1ampactivatedproteinkinases pages 1-3, vis2021nuak1andnuak2 pages 2-3, rooney2025developmentofthe pages 8-8, namiki2011nuak2anemerging pages 2-4).  
Phylogenetic analyses place NUAK2 on an early branch of the SNF1/AMPK superfamily that diverged before the yeast–metazoan split, equidistant from AMPKα isoforms and yeast SNF1 (minchenko2012snf1ampactivatedproteinkinases pages 3-5).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-O-phospho-Ser/Thr (banerjee2014characterizationofwz4003 pages 1-2).

## Cofactor Requirements

Catalytic activity requires divalent metal ions, with Mg²⁺ or Mn²⁺ supporting phosphotransfer, as reported for NUAK-family kinases (palma2023nuak1coordinatesgrowth pages 22-22).

## Substrate Specificity

Documented physiological substrates  
– MYPT1: Ser445, Ser472, Ser910 (banerjee2014characterizationofwz4003 pages 1-2).  
– LATS1 and LATS2 (vis2021nuak1andnuak2 pages 10-12).  
– MRIP, AS160, TBC1D1, SAMS peptide (vis2021nuak1andnuak2 pages 10-12).  
Johnson-style consensus motifs have not been experimentally defined for NUAK2; no explicit motif was reported in recent systematic surveys (rooney2025developmentofthe pages 8-8).

## Structure

Domain organisation: residues 55–306 form the canonical bilobed serine/threonine kinase domain; the C-terminal extension lacks recognizable folded domains (banerjee2014characterizationofwz4003 pages 1-2).  
Key structural elements  
– Gly-rich loop (63–89) and HRD catalytic motif (175–187) (minchenko2012snf1ampactivatedproteinkinases pages 3-5).  
– Activation loop with Thr208, the obligatory LKB1 phosphorylation site (banerjee2014characterizationofwz4003 pages 1-2).  
– Bipartite nuclear-localisation signal 68KKAR71 (minchenko2012snf1ampactivatedproteinkinases pages 3-5).  
3-D models: AlphaFold entry AF-Q9H093-F1 predicts an intact regulatory spine, ordered activation segment, and correctly docked αC-helix typical of active ARK kinases (rooney2025developmentofthe pages 8-8, vis2021nuak1andnuak2 pages 12-14). No experimental crystal structure is currently available.

## Regulation

Post-translational modifications  
– Phosphorylation at Thr208 by the LKB1–STRAD–MO25 complex is required for catalytic activation (banerjee2014characterizationofwz4003 pages 1-2).  
– Autophosphorylation contributes to in-vitro activity (minchenko2012snf1ampactivatedproteinkinases pages 3-5).  
– SCF-βTRCP–dependent poly-ubiquitylation following phospho-degron formation regulates protein turnover (unknownauthors2013phosphorylationubiquitylationand pages 8-10).

Upstream signalling inputs  
– Cellular energy stress (↑AMP/↓ATP), glucose or glutamine deprivation, ER and oxidative stress, UV radiation, and hyperosmotic shock activate NUAK2 (minchenko2012snf1ampactivatedproteinkinases pages 3-5).  
– CaMKK and TAK1 have been implicated as context-specific alternative upstream kinases (minchenko2012snf1ampactivatedproteinkinases pages 3-5, rooney2025developmentofthe pages 8-8).

Transcriptional control  
– TGF-β induces NUAK2 via an intronic SMAD2/3 enhancer (kolliopoulos2019transforminggrowthfactor pages 1-2).  
– NF-κB downstream of CD95 or TNF-α up-regulates transcription (minchenko2012snf1ampactivatedproteinkinases pages 3-5).  
– YAP/TAZ establishes a positive feedback loop that boosts NUAK2 expression (vis2021nuak1andnuak2 pages 7-8).

## Function

Expression patterns: highest basal mRNA levels in gastrointestinal mucosa, kidney, spleen, blood, and cerebellum; inducible in skeletal muscle upon metabolic stress (vis2021nuak1andnuak2 pages 3-5, minchenko2012snf1ampactivatedproteinkinases pages 1-3).

Cellular and signalling roles  
– Stress-response kinase conferring tolerance to glucose starvation and other metabolic insults (minchenko2012snf1ampactivatedproteinkinases pages 3-5).  
– Cytoskeletal regulation: phosphorylates MYPT1 and associates with MRIP, leading to increased myosin light-chain phosphorylation, F-actin destabilisation, and enhanced cell motility (banerjee2014characterizationofwz4003 pages 1-2, namiki2011nuak2anemerging pages 2-4).  
– Hippo pathway modulation: phosphorylates LATS1/2, promotes YAP1 nuclear localisation, and is essential for neural tube closure (vis2021nuak1andnuak2 pages 10-12, vis2021nuak1andnuak2 pages 7-8).  
– TGF-β signalling: binds SMAD3 and TβRI, stabilises SMAD3, and amplifies expression of extracellular-matrix genes (kolliopoulos2019transforminggrowthfactor pages 1-2).  
– NF-κB-mediated anti-apoptotic signalling downstream of CD95/TNF-α protects tumour cells from apoptosis and supports invasive behaviour (minchenko2012snf1ampactivatedproteinkinases pages 3-5).  
– Skeletal muscle: mediates contraction-stimulated glucose transport and protects myocytes from apoptosis (minchenko2012snf1ampactivatedproteinkinases pages 17-19).

## Inhibitors

– WZ4003: ATP-competitive; IC₅₀ ≈ 100 nM for NUAK2 with high kinome selectivity (banerjee2014characterizationofwz4003 pages 1-2).  
– HTH-01-015: NUAK1-selective, negligible activity on NUAK2, useful for isoform differentiation (banerjee2014characterizationofwz4003 pages 1-2).  
– Additional pyrido-pyrimidin-7-one derivatives (e.g., XMD-18-42) inhibit NUAK family kinases with varying selectivity (unknownauthors2013phosphorylationubiquitylationand pages 7-8).

## Other Comments

Disease associations  
– Gene amplification at 1q32 correlates with tumour thickness and poor prognosis in acral melanoma (namiki2011nuak2anemerging pages 2-4).  
– Elevated expression associates with adverse outcome in gliomas (banerjee2014characterizationofwz4003 pages 8-10).  
– NUAK2 up-regulation drives YAP-dependent hepatocellular carcinoma and cutaneous tumour growth (vis2021nuak1andnuak2 pages 15-15).  
– A recessive kinase-dead 22 bp deletion + 1 bp insertion causes human anencephaly by disrupting Hippo signalling (vis2021nuak1andnuak2 pages 7-8).  
– NUAK2 contributes to breast-cancer invasiveness and hepatic fibrosis through TGF-β pathway amplification (kolliopoulos2019transforminggrowthfactor pages 1-2).

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