## Phylogeny

NUAK2 (also called SNARK or Omphalocele kinase 2) is a member of 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 (Banerjee et al., 2014; van de Vis et al., 2021). Orthologues are reported in Mus musculus, Rattus norvegicus, Danio rerio, Drosophila melanogaster and Caenorhabditis elegans (unc-82); yeast SNF1 serves as an out-group for the ARK lineage (Minchenko & Minchenko, 2012; van de Vis et al., 2021; Rooney et al., 2025; Namiki et al., 2011). Phylogenetic analyses place NUAK2 on an early branch of the SNF1/AMPK superfamily that diverged before the yeast–metazoan split, approximately equidistant from mammalian AMPKα isoforms and yeast SNF1 (Minchenko & Minchenko, 2012).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-O-phospho-Ser/Thr (Banerjee et al., 2014).

## Cofactor Requirements

Catalytic activity requires divalent metal ions; Mg²⁺ or Mn²⁺ can support phosphotransfer (Palma et al., 2023).

## Substrate Specificity

Documented physiological substrates include MYPT1 (Ser445, Ser472, Ser910), LATS1, LATS2, MRIP, AS160, TBC1D1 and the synthetic SAMS peptide (Banerjee et al., 2014; van de Vis et al., 2021). No consensus phosphorylation motif has been defined in systematic surveys (Rooney et al., 2025).

## Structure

Residues 55–306 form the canonical bilobed serine/threonine kinase domain; the C-terminal extension lacks recognizable folded domains (Banerjee et al., 2014). Key motifs include the Gly-rich loop (63–89), the catalytic HRD motif (175–187), and the activation loop containing Thr208, the obligatory LKB1 phosphorylation site (Banerjee et al., 2014; Minchenko & Minchenko, 2012). A bipartite nuclear-localisation signal (68KKAR71) is present (Minchenko & Minchenko, 2012). AlphaFold model AF-Q9H093-F1 predicts an intact regulatory spine, an ordered activation segment and a correctly docked αC-helix typical of active ARK kinases; no experimental crystal structure is available (Rooney et al., 2025; van de Vis et al., 2021).

## Regulation

• Activation-loop phosphorylation: Thr208 is phosphorylated by the LKB1–STRAD–MO25 complex and is essential for activity (Banerjee et al., 2014).  
• Autophosphorylation enhances in-vitro activity (Minchenko & Minchenko, 2012).  
• Protein turnover: SCF-βTRCP-dependent poly-ubiquitylation following phospho-degron formation promotes degradation (Unknown authors, 2013).  
• Upstream stimuli: cellular energy stress, nutrient deprivation, ER/oxidative stress, UV irradiation and hyperosmotic shock activate NUAK2 (Minchenko & Minchenko, 2012).  
• Alternative upstream kinases: CaMKK and TAK1 can phosphorylate/activate NUAK2 in specific contexts (Minchenko & Minchenko, 2012; Rooney et al., 2025).  
• Transcriptional control: TGF-β (via an intronic SMAD2/3 enhancer), NF-κB downstream of CD95/TNF-α, and a YAP/TAZ-dependent positive feedback loop up-regulate NUAK2 expression (Kolliopoulos et al., 2019; Minchenko & Minchenko, 2012; van de Vis et al., 2021).

## Function

Expression is highest in gastrointestinal mucosa, kidney, spleen, blood and cerebellum, and is inducible in skeletal muscle during metabolic stress (van de Vis et al., 2021; Minchenko & Minchenko, 2012). Reported cellular roles include:  
• Metabolic stress tolerance and survival during glucose starvation (Minchenko & Minchenko, 2012).  
• Cytoskeletal regulation: phosphorylation of MYPT1 and association with MRIP increase myosin light-chain phosphorylation, destabilise F-actin and enhance cell motility (Banerjee et al., 2014; Namiki et al., 2011).  
• Hippo pathway modulation: phosphorylation of LATS1/2 promotes YAP nuclear localisation and is required for neural tube closure (van de Vis et al., 2021).  
• TGF-β signalling: binding to SMAD3 and TβRI stabilises SMAD3 and amplifies extracellular-matrix gene expression (Kolliopoulos et al., 2019).  
• NF-κB-mediated anti-apoptotic signalling downstream of CD95/TNF-α (Minchenko & Minchenko, 2012).  
• Skeletal muscle: mediates contraction-stimulated glucose transport and protects myocytes from apoptosis (Minchenko & Minchenko, 2012).

## Inhibitors

• WZ4003: ATP-competitive inhibitor, IC₅₀ ≈ 100 nM for NUAK2 with high kinome selectivity (Banerjee et al., 2014).  
• HTH-01-015: NUAK1-selective, negligible activity on NUAK2, useful for isoform discrimination (Banerjee et al., 2014).  
• Additional pyrido-pyrimidin-7-one derivatives (e.g., XMD-18-42) inhibit NUAK family kinases with variable selectivity (Unknown authors, 2013).

## Other Comments

Disease links include gene amplification at 1q32 in acral melanoma, association with poor prognosis in gliomas, YAP-dependent hepatocellular and cutaneous tumour growth, a recessive kinase-dead mutation causing human anencephaly, and roles in breast-cancer invasiveness and hepatic fibrosis via TGF-β pathway amplification (Namiki et al., 2011; Banerjee et al., 2014; van de Vis et al., 2021; Kolliopoulos et al., 2019).

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