## Phylogeny

• Member of the AMP-activated protein kinase (AMPK)-related subfamily within the Ca²⁺/calmodulin-dependent protein kinase (CAMK) group of the human kinome (manning2002theproteinkinase pages 3-3).  
• Forms a 14-kinase clade together with NUAK2, BRSK1/2, SIK1-3, MARK1-4, MELK, QIK and QSK (minchenko2012snf1ampactivatedproteinkinases pages 1-3).  
• Closest paralog NUAK2 shares 58 % overall identity and 82 % identity across the catalytic domain (faisal2020developmentandtherapeutic pages 1-2).  
• Representative orthologs: Mus musculus Nuak1, Rattus norvegicus Nuak1, Danio rerio nuak1, Xenopus spp. nuak1, Drosophila melanogaster Nuak, Caenorhabditis elegans UNC-82 and the distant yeast AMPK ortholog Snf1 (minchenko2012snf1ampactivatedproteinkinases pages 15-17, faisal2020developmentandtherapeutic pages 2-3).

## Reaction Catalyzed

ATP + [protein] → ADP + [protein]-O-phospho-Ser/Thr (banerjee2014characterizationofwz4003 pages 3-4).

## Cofactor Requirements

• Requires Mg²⁺ for ATP coordination, as indicated by in-vitro kinase assays performed in Mg²⁺/ATP buffer (banerjee2014characterizationofwz4003 pages 3-4).

## Substrate Specificity

• Prefers serine/threonine residues within an RSX-S*/T*-XP consensus motif that creates a 14-3-3 docking site; exemplified by phosphorylation of PPP1R12A/MYPT1 at Ser445, Ser472 and Ser910 (unknownauthors2013phosphorylationubiquitylationand pages 35-39, zagorska2010newrolesfor pages 5-5).  
• Similar motif recognition underlies phosphorylation of LATS1 at Ser464 and related PP1 regulatory subunits (banerjee2014interplaybetweenpolo pages 17-17).

## Structure

• Domain organisation:  
– N-terminal bilobal kinase domain (≈ residues 1-270) containing catalytic Lys84 and activation-loop Thr211 (molina2021nuakkinasesbrain–ovary pages 5-6).  
– Central linker.  
– C-terminal regulatory tail (≈ residues 350-661) with three GILK motifs for PP1β binding and the Akt site Ser600 (molina2021nuakkinasesbrain–ovary pages 5-6, banerjee2014interplaybetweenpolo pages 17-17).  
• Lacks the ubiquitin-associated (UBA) domain present in several other AMPK-related kinases (faisal2020developmentandtherapeutic pages 2-3).  
• No experimental crystal or NMR structure is available; AlphaFold model AF-O60285-F1 and homology models reproduce the canonical protein-kinase fold, including an ordered C-helix and hydrophobic spine (rooney2025developmentofthe pages 1-2).  
• Ala195, immediately preceding the DFG motif, lines the ATP pocket; the A195T mutant confers inhibitor resistance without impairing basal catalysis (banerjee2014characterizationofwz4003 pages 4-6).

## Regulation

• Activating phosphorylation events:  
– Thr211 by the LKB1-STRAD-MO25 complex (minchenko2012snf1ampactivatedproteinkinases pages 15-17).  
– Ser600 by AKT1 during glucose starvation and IGF-1 signalling (molina2021nuakkinasesbrain–ovary pages 5-6, vis2021nuak1andnuak2 pages 8-10).  
– Thr211 also targeted by NDR2 downstream of IGF-1 (unknownauthors2017investigatingthefunction pages 40-43).  
• PP1β-MYPT1 interaction via three GILK motifs promotes dephosphorylation of the activation loop, tempering kinase activity (banerjee2014interplaybetweenpolo pages 17-17).  
• Ubiquitylation control:  
– Phosphorylated ESGYYS degron recruits SCF^βTRCP, driving proteasomal degradation (unknownauthors2013phosphorylationubiquitylationand pages 145-150).  
– Atypical K29/K33-linked polyubiquitin chains inhibit catalytic activity (unknownauthors2013phosphorylationubiquitylationand pages 35-39).  
– Deubiquitylase USP9X removes ubiquitin chains and stabilises NUAK1 (minchenko2012snf1ampactivatedproteinkinases pages 1-3).

## Function

• Expression: highly expressed in cerebellum, heart and skeletal muscle; localises to nucleus and cytoskeleton (molina2021nuakkinasesbrain–ovary pages 5-6, unknownauthors2017investigatingthefunction pages 35-40).  
• Upstream regulation: transcriptional and post-translational activation by NF-κB, PI3K/AKT and CD95/Fas pathways (molina2021nuakkinasesbrain–ovary pages 6-8).  
• Confirmed substrates and cellular outcomes:  
– PPP1R12A/MYPT1: phosphorylation induces 14-3-3 binding, inhibits myosin phosphatase, increases MLC2 phosphorylation and reduces focal adhesions, facilitating detachment (zagorska2010newrolesfor pages 5-6).  
– LATS1 Ser464: phosphorylation stabilises LATS1, limiting polyploidy and triggering senescence (minchenko2012snf1ampactivatedproteinkinases pages 1-3).  
– p53 Ser15/392: enhances CDKN1A transcription and metabolic-stress survival (vis2021nuak1andnuak2 pages 8-10).  
– ATM and CASP6: phosphorylation promotes survival during glucose deprivation and modulates apoptosis (vis2021nuak1andnuak2 pages 8-10).  
• Pathway integration: regulates Hippo (via LATS1), actomyosin contractility (via MYPT1/MLC2), mTORC1 (via Raptor), and promotes MMP-2/-9 secretion linked to tumour invasion (molina2021nuakkinasesbrain–ovary pages 6-8).

## Inhibitors

• WZ4003 – ATP-competitive tool compound; IC₅₀ = 20 nM (NUAK1) and 100 nM (NUAK2); blocks MYPT1 Ser445 phosphorylation (banerjee2014characterizationofwz4003 pages 1-2).  
• HTH-01-015 – highly selective; IC₅₀ = 100 nM for NUAK1 with >100-fold selectivity over NUAK2; A195T mutation confers ~50-fold resistance (banerjee2014characterizationofwz4003 pages 4-6).  
• BX-795 – potent but non-selective; IC₅₀ ≈ 5 nM for NUAK1 with significant off-target activity (faisal2020developmentandtherapeutic pages 11-12).  
• XMD-18-42 / XMD-18-83 – nanomolar inhibitors with off-target Aurora kinase activity (unknownauthors2013phosphorylationubiquitylationand pages 103-113).  
• Emerging pyrido[2,3-d]pyrimidin-7(8H)-one series shows improved potency and brain penetration in preclinical models (rooney2025developmentofthe pages 1-2).

## Other Comments

• Gene amplification or over-expression occurs in brain, melanoma, breast, ovarian, cervical, prostate, gastric, lung and nasopharyngeal cancers and correlates with poor prognosis (molina2021nuakkinasesbrain–ovary pages 6-8).  
• Functionally relevant mutations: Lys84Ala abolishes catalysis; Thr211Ala prevents LKB1 activation; Ser600Ala eliminates AKT1 activation; Ile400Lys/Leu401Lys disrupt PP1β interaction; Ala195Thr confers resistance to ATP-competitive inhibitors (molina2021nuakkinasesbrain–ovary pages 5-6, banerjee2014characterizationofwz4003 pages 4-6).

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