## Proposed EC/sub-subclass

2.7.11.–

## Accepted name

Serine/threonine-protein kinase STK38L (NDR2)

## Synonyms

NDR2; STK38L; Nuclear Dbf2-related protein kinase 2; LATS-related kinase 2

## Phylogeny

Member of the NDR (nuclear Dbf2-related) subgroup of the AGC serine/threonine kinase family, highly conserved from yeast to humans (Bichsel et al., 2004; Cornils, 2010). The human NDR branch comprises NDR1 (STK38), NDR2 (STK38L), LATS1 and LATS2 (Cornils, 2010). Orthologues include S. cerevisiae Dbf2p/Dbf20p/Cbk1p, S. pombe Sid2p/Orb6p, C. elegans SAX-1/LATS, and D. melanogaster Tricornered/Warts (Bichsel et al., 2004; Cornils, 2010; Martin & Camonis, 2021). Upstream Ste20-like kinases MST1/2/3 are closely related and act as activators (Stegert et al., 2005).

## Reaction catalyzed

ATP + [a protein] ⇌ ADP + [a phosphoprotein] (Cornils, 2010; Hergovich et al., 2008).

## Cofactor requirements

Requires Mg²⁺ for ATP binding and phosphoryl transfer; 10 mM MgCl₂ is used in vitro (Bichsel et al., 2004; Hergovich et al., 2008; Stegert et al., 2005).

## Specificity

Prefers basophilic motifs with basic residues N-terminal to the phospho-acceptor. Consensus sequences reported include H-X-R-R-X-S/T, H-R-x-x-S/T, HXRXXS/T, and [R/K]-X-[pS/pT]-[L/V] (Johnson et al., 2023; Hergovich, 2016). A synthetic peptide, KKRNRRLSVA, is efficiently phosphorylated in vitro (Stegert, 2005; Köhler, 2012).

## Structure

Composed of:  
• N-terminal regulatory (NTR) domain that binds MOB proteins and S100B (Cornils, 2010).  
• Central catalytic kinase domain with 12 conserved subdomains (Cornils, 2010).  
• C-terminal hydrophobic motif (HM) containing Thr442 (Cornils, 2010; Martin, 2020).  
A 30–60 aa insertion between subdomains VII and VIII harbours an auto-inhibitory sequence rich in basic residues (Bichsel et al., 2004; Cornils, 2010). Crystal structures of the paralog STK38 show an elongated activation segment and an auto-inhibitory αC helix (Martin & Camonis, 2021). AlphaFold models recapitulate these features (Martin, 2020).

## Regulation

Phosphorylation-dependent activation:  
• Ser282 (activation loop) – autophosphorylation, essential for activity (Cornils, 2010).  
• Thr442 (HM) – phosphorylated by MST1/2/3; MST3 enhances activity ~10-fold (Stegert et al., 2005).  
• Thr74/Thr75 (NTR) – required for full activity (Martin, 2020; Martin & Camonis, 2021).

Dephosphorylation: PP2A inactivates STK38L (Martin, 2020; Martin & Camonis, 2021).

Regulatory proteins:  
• MOB1A/B act as co-activators by binding the NTR and relieving auto-inhibition, whereas MOB2 is inhibitory (Cornils, 2010; Hergovich et al., 2008; Köhler, 2012).  
• S100B binds the NTR and can stimulate activity in vitro (Bichsel et al., 2004).

Other post-translational modifications: ISGylation, ubiquitination and acetylation have been reported (Hergovich, 2016).

## Function

Participates in cell-cycle progression, centrosome duplication, cell morphology, spreading, neurite outgrowth and mitotic chromosome alignment (Bichsel et al., 2004; Stegert, 2005; Hergovich, 2013). Localises predominantly in the cytoplasm (Stegert, 2005). Highly expressed in rapidly proliferating tissues such as stomach and intestine (Stegert, 2005).

Signalling context:  
Upstream kinases – MST1-5, MAP4K family (Cornils, 2010; Martin, 2020).  
Downstream substrates – YAP (Ser127), TAZ, Rabin8, HP1α, XPO1 (Hergovich, 2016; Martin & Camonis, 2021).  
Pathway – Acts within the Hippo pathway to restrain YAP/TAZ activity (Bichsel et al., 2004; Hergovich, 2016).

## Inhibitors

No direct small-molecule inhibitors reported; selective nuclear export inhibitors such as Selinexor target the substrate XPO1 (Martin, 2020).

## Other comments

STK38L lies in the cancer-associated 12p11 amplicon. Up-regulation is observed in aggressive breast cancers, melanomas and metastatic lung cancer lines (Bichsel et al., 2004; Stegert, 2005). Intestinal Ndr1/2 knockout mice display hyperplasia and increased tumour incidence (Hergovich, 2016). An exonic SINE insertion in canine STK38L causes early retinal degeneration (Hergovich, 2013).

## References

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