## Phylogeny

WNK2 is one of four human WNK paralogues that constitute the “Other-group” protein kinase subfamily in which the catalytic lysine is repositioned from β-strand 3 to β-strand 2 (Min et al., 2004; With No Lysine (WNK) Family, 2011). Orthologues are present throughout vertebrates (mouse, rat and zebrafish wnk2a/wnk2b), and within the WNK branch WNK2 clusters more closely with WNK1 and WNK3 than with WNK4 (McCormick & Ellison, 2011; With No Lysine (WNK) Family, 2011).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-Ser/Thr-P (With No Lysine (WNK) Family, 2011).

## Cofactor Requirements

Catalytic activity is Mg²⁺-dependent (Min et al., 2004).

## Substrate Specificity

Large-scale phosphoproteomics revealed a limited substrate spectrum without a clear sequence consensus (Johnson et al., 2023). Biochemical data demonstrate direct phosphorylation of OSR1 and SPAK via RFXV-dependent docking, with a low catalytic turnover (k\_cat ≈ 0.05 min⁻¹) compared with WNK1/3 (With No Lysine (WNK) Family, 2011).

## Structure

The 2 180-residue protein comprises an N-terminal kinase domain (~1–365), an autoinhibitory segment (675–743), several coiled-coil and PxxP motifs, and a C-terminal membrane-targeting region (1922–2156) (McCormick & Ellison, 2011; With No Lysine (WNK) Family, 2011). No experimental WNK2 structure is available; homology models and AlphaFold (AF-Q9Y3S1-F1) show the typical bilobal fold, β2-lysine, displaced C-helix, expanded ATP pocket and conserved chloride-binding cavity described for WNK1 (Min et al., 2004; With No Lysine (WNK) Family, 2011). The activation loop contains Ser356, required for activity, and adopts an active-like DFG conformation (WNK kinase signalling in cancer biology, 2010; With No Lysine (WNK) Family, 2011).

## Regulation

• Autophosphorylation on Ser338 and Ser356 is necessary for full activity (With No Lysine (WNK) Family, 2011; Identifying Novel Functions of the WNK Pathway, 2017).  
• KLHL3–CUL3-mediated poly-ubiquitination targets WNK2 for proteasomal degradation (With No Lysine (WNK) Family, 2011; Identifying Novel Functions of the WNK Pathway, 2017).  
• An internal autoinhibitory domain suppresses kinase output and can inhibit other WNK isoforms (With No Lysine (WNK) Family, 2011).  
• Binding of intracellular Cl⁻ to the conserved cavity favours an inactive state, coupling activity to ionic strength (With No Lysine (WNK) Family, 2011).  
• Promoter CpG hypermethylation down-regulates WNK2 expression in several cancers (McCormick & Ellison, 2011; With No Lysine (WNK) Family, 2011; Identifying Novel Functions of the WNK Pathway, 2017).  
• Phosphorylation by Akt1/SGK1 further modulates activity (Identifying Novel Functions of the WNK Pathway, 2017).

## Function

WNK2 is abundantly expressed in brain, heart and colonic epithelium but low in kidney-derived cell lines (McCormick & Ellison, 2011; With No Lysine (WNK) Family, 2011). Acting upstream of OSR1 and SPAK, it controls SLC12A family cotransporters: activation of NKCCs and inhibition of KCCs regulates electrolyte balance and cell volume (Richardson & Alessi, 2008; With No Lysine (WNK) Family, 2011). WNK2 also stimulates the MEKK2/3→ERK5 MAPK pathway and suppresses EGF-induced ERK1/2 signalling, thereby restraining G1/S progression (With No Lysine (WNK) Family, 2011). Autophosphorylation is triggered by osmotic or chloride stress (Identifying Novel Functions of the WNK Pathway, 2017).

## Inhibitors

WNK463 is a pan-WNK ATP-competitive inhibitor with an IC₅₀ of ~1 nM against WNK2 and negligible off-target activity across 443 kinases at 10 µM (Yamada et al., 2016).

## Other Comments

Promoter hypermethylation or chromosomal loss identifies WNK2 as a tumour-suppressor gene in glioma and meningioma; re-expression curbs colony formation and Rac1-dependent invasion independently of kinase activity (McCormick & Ellison, 2011; With No Lysine (WNK) Family, 2011; Identifying Novel Functions of the WNK Pathway, 2017). No Mendelian disease-causing variants have been reported, and WNK2 is not mutated in pseudohypoaldosteronism type II (Zhang et al., 2016).

## References

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