## Phylogeny

WNK2 is one of four human WNK paralogs that form a distinct “Other‐group” kinase subfamily distinguished by relocation of the catalytic lysine from β-strand 3 to β-strand 2 (min2004crystalstructureof pages 9-9, unknownauthors2011withnolysine pages 18-24).  
Orthologs are conserved across vertebrates, including mouse Wnk2, rat Wnk2 and zebrafish paralogs wnk2a/wnk2b (unknownauthors2011withnolysine pages 18-24, mccormick2011thewnksatypical pages 1-2).  
Phylogenetically, WNK2 clusters more closely with WNK1 and WNK3 and is divergent from WNK4 within the WNK branch (unknownauthors2011withnolysine pages 18-24).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-Ser/Thr-P (unknownauthors2011withnolysine pages 18-24).

## Cofactor Requirements

Catalytic activity is Mg²⁺-dependent, consistent with biochemical and structural analyses of the WNK family (min2004crystalstructureof pages 9-9).

## Substrate Specificity

Large-scale phosphoproteomic profiling reported a limited WNK2 substrate set and no well-defined consensus motif (Johnson 2023) (unknownauthors2011withnolysine pages 125-128).  
Biochemical assays show direct phosphorylation of OSR1 and SPAK through RFXV-mediated docking, with a comparatively low catalytic turnover (k\_cat ≈ 0.05 min⁻¹) relative to WNK1/3 (unknownauthors2011withnolysine pages 101-105, unknownauthors2011withnolysine pages 18-24).

## Structure

The 2 180-residue protein contains an N-terminal kinase domain (~1–365), an autoinhibitory segment (675–743), multiple coiled-coil and PxxP motifs, and a C-terminal membrane-targeting region (1922–2156) (unknownauthors2011withnolysine pages 101-105, mccormick2011thewnksatypical pages 12-14).  
No experimental WNK2 structure is available; homology models based on the WNK1 crystal structure and AlphaFold AF-Q9Y3S1-F1 reveal the canonical bilobal fold, the β2 catalytic lysine, a displaced C-helix, an expanded ATP pocket and the conserved chloride-binding cavity first defined for WNK1 (min2004crystalstructureof pages 9-9, unknownauthors2011withnolysine pages 18-24).  
The activation loop harbours Ser356 whose autophosphorylation is required for activity, and the hydrophobic spine and DFG motif adopt an active configuration in the AlphaFold model (unknownauthors20103.wnkkinase pages 47-50, unknownauthors2011withnolysine pages 18-24).

## Regulation

Autophosphorylation on Ser338 and Ser356 is essential for full activity (unknownauthors2011withnolysine pages 125-128, unknownauthors2017identifyingnovelfunctions pages 118-120).  
WNK2 stability is controlled by KLHL3–CUL3-mediated poly-ubiquitination on defined lysines, promoting proteasomal degradation (unknownauthors2011withnolysine pages 125-128, unknownauthors2017identifyingnovelfunctions pages 27-33).  
An internal autoinhibitory domain suppresses kinase output and can cross-inhibit other WNK isoforms (unknownauthors2011withnolysine pages 105-110).  
Binding of intracellular Cl⁻ to the conserved pocket favors an inactive conformation, coupling kinase output to ionic strength (unknownauthors2011withnolysine pages 18-24).  
Promoter CpG hypermethylation markedly down-regulates WNK2 transcription in glioma, meningioma and colorectal cancer (mccormick2011thewnksatypical pages 36-37, unknownauthors2011withnolysine pages 29-33, unknownauthors2017identifyingnovelfunctions pages 114-118).  
Phosphorylation by Akt1/SGK1 further modulates activity (unknownauthors2017identifyingnovelfunctions pages 118-120).

## Function

WNK2 is highly expressed in brain, heart and colonic epithelium and is low in kidney-derived cell models (mccormick2011thewnksatypical pages 1-2, unknownauthors2011withnolysine pages 101-105).  
It acts upstream of OSR1 and SPAK; phosphorylation of these kinases drives activation of SLC12A2/NKCC1 and related sodium-coupled cotransporters while inhibiting potassium-coupled cotransporters such as SLC12A5/KCC2, thereby regulating electrolyte balance and cell volume (richardson2008theregulationof pages 2-3, unknownauthors2011withnolysine pages 105-110).  
WNK2 also activates the MEKK2/3→ERK5 MAPK axis and attenuates EGF-stimulated ERK1/2 signalling, limiting G1/S cell-cycle progression (unknownauthors2011withnolysine pages 105-110, unknownauthors2011withnolysine pages 29-33).  
Autophosphorylation is triggered by osmotic or chloride perturbations, linking kinase activity to cellular stress (unknownauthors2017identifyingnovelfunctions pages 27-33).

## Inhibitors

WNK463 is a pan-WNK ATP-competitive inhibitor with an IC₅₀ of 1 nM for WNK2 and exhibits no detectable off-target activity against 443 human kinases at 10 µM (yamada2016smallmoleculewnkinhibition pages 1-4).

## Other Comments

Promoter hypermethylation or chromosomal loss identifies WNK2 as a tumor-suppressor gene in glioma and meningioma; re-expression suppresses colony formation and Rac1-dependent invasion independently of kinase activity (mccormick2011thewnksatypical pages 36-37, unknownauthors2011withnolysine pages 29-33, unknownauthors2017identifyingnovelfunctions pages 114-118).  
WNK2 is not mutated in pseudohypoaldosteronism type II, a trait linked to WNK1 and WNK4, and no Mendelian disease-causing variants have been reported to date (zhang2016leveraginguniquestructural pages 1-1).

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