## Phylogeny

VRK3 is one of three metazoan Vaccinia-related kinases (VRK1–3) that form a distinct branch within the “Other” group of the human kinome because their catalytic motifs diverge from those of canonical casein-kinase-like enzymes (Scheeff et al., 2009). The subfamily is distantly related to the pox-viral B1R kinase (Scheeff et al., 2009) and is evolutionarily conserved, with orthologs reported in human, mouse, rat, zebrafish, fruit-fly and nematode genomes (Nichols & Traktman, 2004; Vaccinia-related kinase signaling, 2010).

## Reaction Catalyzed

ATP + barrier-to-autointegration factor (Ser4) ⇌ ADP + barrier-to-autointegration factor (Ser4-P) (Park et al., 2015).

## Cofactor Requirements

BAF phosphorylation in vitro requires a divalent metal ion; the specific cation was not identified (Park et al., 2015).

## Substrate Specificity

Only one high-confidence substrate has been validated: BAF, phosphorylated exclusively on Ser4. Large-scale profiling failed to uncover additional targets, and a consensus recognition motif has not been established (Park et al., 2015; Scheeff et al., 2009).

## Structure

• Residues 1–147: intrinsically disordered N-terminus bearing a bipartite nuclear-localisation signal (Moura et al., 2016).  
• Residues 148–472: kinase-like domain; crystal structures PDB 2V62 and 2JII reveal a canonical bilobal fold locked in a closed conformation by a unique αC4 helix (Scheeff et al., 2009).  
• Full-length model available from AlphaFold (AF-Q8IV63-F1).

Key features  
– Catalytic motifs are degenerated (TRDNQG glycine loop; Lys201→Ser; HRD Asp→Asn306; DFG Asp→Gly326) and ATP binding is sterically blocked by Asp175, Gln177 and Phe313, classifying VRK3 as a pseudokinase (Scheeff et al., 2009).  
– Despite loss of catalysis, stabilising elements such as the Lys203-Glu214 ion pair and the hydrophobic spine are retained, conferring high thermal stability (Scheeff et al., 2009).  
– A conserved surface patch on the C-lobe serves as a docking interface for VHR phosphatase and other partners (Scheeff et al., 2009).

## Regulation

Post-translational modification  
• Stress-activated CDK5 phosphorylates VRK3, potentiating activation of the VHR phosphatase (Liu et al., 2019).

Protein interactions / allostery  
• Binding of BAF to the disordered N-terminus induces conformational changes that enable Ser4 phosphorylation (Park et al., 2015).  
• VRK3 forms a scaffold with VHR (DUSP3) and ERK, accelerating VHR-mediated ERK dephosphorylation (Scheeff et al., 2009).  
• Interacts with GDP-bound Ran GTPase; functional consequences remain unclear (Moura et al., 2016).

Expression and localisation  
• mRNA is enriched during murine embryonic haematopoiesis and in adult liver, kidney, muscle, thymus and bone marrow; lower in spleen (Moura et al., 2016).  
• Protein abundance peaks at the G1/S transition, in contrast to mitotic peaking of VRK1 (Park et al., 2015).  
• The intrinsic NLS targets VRK3 to the nucleoplasm (Moura et al., 2016).

## Function

• Nuclear-envelope dynamics: BAF Ser4 phosphorylation by VRK3 supports envelope disassembly/reassembly during interphase (Park et al., 2015).  
• MAPK signalling: VRK3 activates VHR, leading to dephosphorylation and timely inactivation of nuclear ERK1/2 (Scheeff et al., 2009; Moura et al., 2016).  
• Stress response: Under glutamate stress, CDK5-modified VRK3 promotes nuclear import of HSP70, reinforcing ERK suppression (Liu et al., 2019).  
• Cell-cycle control: Over-expression accelerates S-phase entry, whereas knock-down delays proliferation (Park et al., 2015).

## Other Comments

The VRK3 gene maps to chromosome 19q13.33, and no germline or somatic disease-linked mutations have been reported (Vázquez-Cedeira et al., 2012; Moura et al., 2016).

## 9. References

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