## Phylogeny

• Member of the Vaccinia-related kinase (VRK) subfamily together with the active kinases VRK1 and VRK2; the family is distantly related to the pox-viral B1R kinase (scheeff2009structureofthe pages 1-2).  
• According to the human kinome classification, VRKs occupy a distinct branch assigned to the “Other” group because their catalytic motifs diverge from canonical Casein Kinase 1 residues (scheeff2009structureofthe pages 1-2).  
• Orthologs authenticated in Homo sapiens, Mus musculus, Rattus norvegicus, Danio rerio, Drosophila melanogaster and Caenorhabditis elegans, indicating conservation across metazoans (nichols2004characterizationofthree pages 5-6, unknownauthors2010vacciniarelatedkinase(vrk) pages 1-4).

## Reaction Catalyzed

ATP + barrier-to-autointegration factor (Ser4) → ADP + barrier-to-autointegration factor (Ser4-P) (park2015presumedpseudokinasevrk3 pages 3-4).

## Cofactor Requirements

Divalent cations are required in vitro for BAF phosphorylation; the specific metal ion was not disclosed (park2015presumedpseudokinasevrk3 pages 3-4).

## Substrate Specificity

• Confirmed substrate: BAF, single phosphorylation site Ser4 (park2015presumedpseudokinasevrk3 pages 10-11).  
• A consensus recognition motif has not been defined; large-scale specificity studies report no additional high-confidence targets (scheeff2009structureofthe pages 7-8).

## Structure

Domain organisation  
– Residues 1-147: intrinsically disordered N-terminal segment containing a bipartite nuclear localisation signal (moura2016vrk3 pages 1-3).  
– Residues 148-472: kinase-like domain solved by X-ray crystallography (PDB 2V62, PDB 2JII) (scheeff2009structureofthe pages 10-11).  
– Full-length AlphaFold model: AF-Q8IV63-F1 (scheeff2009structureofthe pages 5-7).

Key structural features  
• Conserves the bilobal kinase fold and a unique αC4 helix that locks the lobes in a closed conformation (scheeff2009structureofthe pages 2-3).  
• Catalytic motifs are degraded: G-loop TRDNQG replaces GxGxxG; VAIK Lys → Ser201; HRD Asp → Asn306; DFG Asp → Gly326 (scheeff2009structureofthe pages 3-4, scheeff2009structureofthe pages 5-7).  
• Occluding residues Asp175, Gln177 and Phe313 fill the ATP-binding pocket, abolishing nucleotide binding (scheeff2009structureofthe pages 3-4).  
• Stabilising elements such as the K203–E214 ion pair and hydrophobic spine remain intact, conferring high thermal stability (scheeff2009structureofthe pages 4-5).  
• A conserved surface patch on the back of the C-lobe forms the docking interface for VHR and other partners (scheeff2009structureofthe pages 7-8).

## Regulation

Post-translational modifications  
• Stress-activated CDK5 phosphorylates VRK3, enhancing VHR activation; precise residue(s) not mapped (liu2019phosphoproteomicanalysesof pages 11-12).

Allosteric and protein-mediated control  
• Binding of BAF to the N-terminal segment induces conformational changes that permit Ser4 phosphorylation (park2015presumedpseudokinasevrk3 pages 7-9).  
• VRK3 directly binds VHR (DUSP3) and scaffolds ERK, facilitating VHR-mediated ERK dephosphorylation (scheeff2009structureofthe pages 7-8).  
• Interacts with GDP-bound Ran GTPase; functional outcome not resolved (moura2016vrk3 pages 1-3).

Expression dynamics  
• mRNA peaks during murine embryonic haematopoiesis and is high in adult liver, kidney, muscle, thymus and bone marrow, with lower levels in spleen (moura2016vrk3 pages 1-3).  
• Protein abundance rises at G1/S, contrasting with VRK1, which peaks in mitosis (park2015presumedpseudokinasevrk3 pages 3-4).  
• Nucleoplasmic localisation driven by the N-terminal NLS (moura2016vrk3 pages 1-3).

## Function

• Nuclear envelope dynamics: phosphorylation of BAF Ser4 supports nuclear envelope disassembly and reassembly during interphase (park2015presumedpseudokinasevrk3 pages 1-2).  
• MAPK signalling: VRK3 activates VHR, leading to nuclear ERK1/2 dephosphorylation and timely termination of ERK activity (scheeff2009structureofthe pages 1-2, moura2016vrk3 pages 3-4).  
• Stress response: under glutamate challenge, CDK5-modified VRK3 promotes HSP70 nuclear import, reinforcing ERK suppression (liu2019phosphoproteomicanalysesof pages 11-12).  
• Cell-cycle progression: over-expression accelerates S-phase entry, whereas knock-down delays proliferation (park2015presumedpseudokinasevrk3 pages 3-4).

## Other Comments

• Gene locus: chromosome 19q13.33 (vazquezcedeira2012vacciniarelatedkinase3(vrk3) pages 1-3).  
• No germline or somatic disease-linked mutations have been reported to date (moura2016vrk3 pages 1-3, vazquezcedeira2012vacciniarelatedkinase3(vrk3) pages 45-46).

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