## Phylogeny

Kalirin belongs to the Dbl family of Rho guanine-nucleotide exchange factors and clusters within the Trio subfamily (Johnson et al., 2000; Ma et al., 2001). It shares ~60 % sequence identity with Trio; both vertebrate genes arose from a single ancestral invertebrate gene that is represented by dTrio in Drosophila melanogaster and Unc-73 in Caenorhabditis elegans (Parnell et al., 2021; Rabiner et al., 2005). Invertebrate orthologues lack the C-terminal protein-kinase domain that is present in vertebrate Kalirin and Trio (Rabiner et al., 2005).  
Classification of the Kalirin kinase domain is inconsistent in the literature: it has been placed in the Ca2+/calmodulin-dependent kinase (CAMK) group (Johnson et al., 2000), in the tyrosine-kinase-like/mixed-lineage kinase (TKL/MLK) family (Parnell et al., 2021), and in the CMGC group within the DYRK family (Manning et al., 2002).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[Kalirin] ⇌ ADP + O-phospho-L-seryl/threonyl-[Kalirin]  
(Parnell et al., 2021; Xin et al., 2008)

## Cofactor Requirements

Mg²⁺ is required for kinase activity; the domain contains a distinctive Mg²⁺-binding loop (DLE in place of the canonical DFG) (Anonymous, 2015; Johnson et al., 2000; Parnell et al., 2021).

## Substrate Specificity

No substrate-specificity data are provided in the supplied nomenclature.

## Structure

Kalirin is a large multidomain protein produced as several isoforms (Kalirin-7, ‑9, ‑12) through alternative promoters and splicing (Parnell et al., 2021; Rabiner et al., 2005).  
Key structural modules include:  
• N-terminal SEC14P lipid-binding domain (Parnell et al., 2021)  
• Multiple spectrin-like repeats that scaffold partner binding (Parnell et al., 2021)  
• Rac-GEF (DH-PH) cassette; PH domain binds GluN2B and TRKA (Parnell et al., 2021)  
• RhoA-GEF (second DH-PH) present in Kalirin-9/-12 (Parnell et al., 2021)  
• Two SH3 domains mediating autoinhibition (Parnell et al., 2021)  
• C-terminal PDZ-binding motif in Kalirin-7 (Parnell et al., 2021)  
• Ig and FN3 domains in Kalirin-12 (Parnell et al., 2021)  
• Ser/Thr kinase domain unique to Kalirin-12; AlphaFold predicts a canonical bilobal fold with an “in” C-helix and an extended activation loop characteristic of an active conformation (Xin et al., 2008; Li et al., 2023; Anonymous, 2015).

## Regulation

Activity is controlled by alternative splicing, numerous phosphorylation events and intramolecular or allosteric interactions (Parnell et al., 2021; Anonymous, 2015).  
Phosphorylation sites/regulators:  
– CaMKII on T95 within SEC14P → ↑Rac-GEF activity (Parnell et al., 2021)  
– Cdk5/p25 on T1590 (Xin et al., 2008)  
– NRG1-ErbB4-Fyn pathway on the PDZ-binding motif (Parnell et al., 2021)  
– Abl1 on spectrin repeats 4-6, promoting calpain cleavage (Anonymous, 2015)  
– Autophosphorylation by its own kinase domain in Kalirin-12 (Parnell et al., 2021)  
Allosteric control: SH3–PXXP contacts dampen GEF activity, and Gαq binding to the PH domain modulates the RhoA-GEF module (Parnell et al., 2021).

## Function

Highly expressed in the nervous system and, to a lesser extent, in smooth-muscle tissue (Parnell et al., 2021). Embryonic neurons predominantly express Kalirin-9/-12, whereas adult cortex and hippocampus mainly express Kalirin-7 (Parnell et al., 2021; Unknown Author, 2012).  
As a dual Rho-GEF, Kalirin activates Rac1 and RhoA to organise the actin cytoskeleton, driving dendritic-spine morphogenesis, axon extension and synaptic plasticity; Rac1–PAK signalling promotes spine enlargement, whereas RhoA performs opposing functions (Parnell et al., 2021). Kalirin also regulates NMDA and AMPA receptor trafficking and is required for NMDAR-dependent LTP and LTD (Parnell et al., 2021).  
Upstream kinases: CaMKII, Cdk5, Fyn and Abl1 (Parnell et al., 2021; Xin et al., 2008; Anonymous, 2015).  
Interacting partners include PSD95, DISC1, GluN2B, neuroligin-1, HAP1, TRKA and Supervillin (Parnell et al., 2021; Remmers et al., 2014).

## Inhibitors

Small molecules targeting its GEF domains have been reported: ITX3 (Rac-GEF inhibitor) and NPPD (RhoA-GEF inhibitor) reduce Rac-dependent neurite outgrowth and limit smooth-muscle cell migration (Parnell et al., 2021). Pharmacological inhibition of Abl1 can indirectly modulate Kalirin function (Anonymous, 2015).

## Other Comments

Kalirin dysregulation is linked to schizophrenia, autism spectrum disorder, Alzheimer’s disease, addiction, intellectual disability, developmental delay, stroke, coronary heart disease, Parkinson’s disease and Huntington’s disease (Parnell et al., 2021; Remmers et al., 2014). Both loss- and gain-of-function mutations have been identified; variants within the RhoA-GEF domain are associated with schizophrenia (Parnell et al., 2021).

## 9. References

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