## Phylogeny

TRIO is an evolutionarily conserved, multidomain signalling protein. Orthologs are found in invertebrates (UNC-73 in Caenorhabditis elegans; D-Trio in Drosophila) and a single vertebrate paralog, Kalirin, is present (Schmidt & Debant, 2014). The N-terminal protein-kinase domain forms a distinct clade that groups with the N-terminal kinase regions of Obscurin/SPEG proteins and shows similarity to the myosin light-chain kinase (MLCK) subgroup (Unknown Authors, 2025, pp. 64–69). Placement of the kinase within the human kinome is debated: it has been assigned to the tyrosine-kinase-like (TKL), atypical, CMGC, or STE groups in different surveys (Debant et al., 1996; Hunter & Manning, 2015). Aside from the kinase, TRIO belongs to the Dbl family of Rho guanine nucleotide-exchange factors (RhoGEFs) (Schmidt & Debant, 2014).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr → ADP + protein-O-phospho-L-Ser/Thr (Unknown Authors, 2025, pp. 64–69; Hunter & Manning, 2015).

## Cofactor Requirements

Catalysis requires ATP and divalent cations, typically Mg²⁺ or Mn²⁺ (Debant et al., 1996; Hunter & Manning, 2015; Unknown Authors, 2025, pp. 64–69).

## Substrate Specificity

• GEF activity: the N-terminal GEF (GEFD1/TrioN) activates Rac1 and RhoG, whereas the C-terminal GEF (GEFD2/TrioC) activates RhoA (Schmidt & Debant, 2014; Katrancha et al., 2017).  
• Kinase activity: TRIO phosphorylates myosin light chain and other cytoskeletal proteins in vitro; preferred sites are reported to contain basic residues flanking the phospho-acceptor (Debant et al., 1996; Unknown Authors, 2025, pp. 44–46). An unbiased consensus was not identified in the Johnson et al. (2023) kinase-substrate atlas.

## Structure

TRIO is a ~324–330 kDa protein composed of an N-terminal Sec14/Cral-Trio lipid-binding module, nine spectrin repeats (S1–S9), two tandem DH-PH GEF modules, a serine/threonine protein-kinase domain and several accessory motifs (two SH3 domains, an Ig-like domain) (Debant et al., 1996; Schmidt & Debant, 2014; Bandekar et al., 2022).  
• Spectrin repeats provide an elongated scaffold; the central catalytic region is globular (Bandekar et al., 2022).  
• Crystal structure of the TrioC DH-PH tandem reveals an autoinhibited conformation where the PH domain blocks RhoA access to the DH domain; the αN helix stabilises this interface (Bandekar et al., 2019).  
• Cryo-EM and AlphaFold models support this configuration and delineate conserved, flexible linker segments that modulate activity (Bandekar et al., 2022; Unknown Authors, 2025, pp. 148–151).

## Regulation

• Post-translational modification: TRIO is phosphorylated only on serine residues; PKC activation enhances phosphorylation (Debant et al., 1996). Tyrosine phosphorylation has not been detected (Schmidt & Debant, 2014).  
• Autoinhibition: both GEF units adopt intramolecularly inhibited states. TrioC autoinhibition is relieved by activated Gαq/11, while spectrin repeats and disordered linkers suppress TrioN until displaced by partner proteins such as DISC1 (Bandekar et al., 2019; Bandekar et al., 2022; Schmidt & Debant, 2014).

## Function

TRIO acts as a signalling hub linking upstream cues to cytoskeletal reorganisation.  
• Expression: ubiquitous but highest in neural tissue, skeletal muscle, heart and immune cells; brain-restricted isoforms (e.g., TRIO9, TrioA-E) predominate (Schmidt & Debant, 2014; Katrancha et al., 2017; Unknown Authors, 2025, pp. 44–46).  
• Upstream regulators: Gαq/11-coupled GPCRs, the LAR receptor phosphatase, and the NOTCH–DAB1–ABL axis (Bandekar et al., 2019; Schmidt & Debant, 2014; Unknown Authors, 2025, pp. 148–151).  
• Interacting partners: DISC1, Kidins220/ARMS, Piccolo, Bassoon (Schmidt & Debant, 2014; Tao et al., 2020; Unknown Authors, 2025, pp. 148–151).  
• Downstream effectors: activates Rac1, RhoG and RhoA to control cell motility, adhesion, axon guidance and morphogenesis (Schmidt & Debant, 2014; Katrancha et al., 2017; Tao et al., 2020).

## Other Comments

Germline and somatic TRIO variants are linked to human disease.  
• Neurodevelopmental disorders: de novo mutations (e.g., K1431M, R1428Q, P1461T, M2145T) alter GEF activity and associate with autism, schizophrenia, intellectual disability and bipolar disorder (Katrancha et al., 2017; Pengelly et al., 2016).  
• Cancer: elevated TRIO expression and mutations that disrupt TrioC autoinhibition enhance RhoA signalling in uveal melanoma; the truncated oncogenic isoform “Tgat” (RhoA-specific DH only) occurs in adult T-cell leukaemia (Schmidt & Debant, 2014; Bandekar et al., 2019).

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