## Phylogeny

Vertebrate orthologs with the full Ig/FnIII–SH3–RhoGEF/PH–dual-kinase scaffold are documented in Mus musculus, Rattus norvegicus, Gallus gallus and Danio rerio (grogan2019unravelingobscurinsin pages 2-4).  
Invertebrate counterparts include Caenorhabditis elegans UNC-89 and Drosophila melanogaster obscurin, the latter possessing a pseudokinase/kinase pair homologous to human SK1/SK2 (manring2017obscurefunctionsthe pages 2-3, zacharchenko2023pk1fromdrosophila pages 2-3).  
Paralogous human MLCK-type giants SPEG and OBSL1 derive from gene duplication; SPEG shares ~40 % sequence identity across the tandem kinase domains (hu2013thekinasedomains pages 1-2).  
Kinome assignment: CAMK group, myosin-light-chain-kinase (MLCK) subfamily, DMT class of cytoskeletal CAMKs (zacharchenko2023pk1fromdrosophila pages 2-3).

## Reaction Catalyzed

Protein-Ser/Thr + ATP ⇌ Protein-O-Ser/Thr-phosphate + ADP (hu2013thekinasedomains pages 1-2, marston2017obscurinvariantsand pages 2-4).

## Cofactor Requirements

Catalytic turnover requires divalent cations, with Mg²⁺ or Mn²⁺ supporting activity typical of MLCK enzymes (hu2013thekinasedomains pages 1-2, randazzo2017thepotentialof pages 27-31).

## Substrate Specificity

Experimentally verified substrates are the cytoplasmic tail of N-cadherin for SK2 and the β₁ subunit of Na⁺/K⁺-ATPase for SK1 (hu2013thekinasedomains pages 1-2, randazzo2017thepotentialof pages 14-16).  
A global consensus phosphorylation motif has not been defined for OBSCN kinases (hu2013thekinasedomains pages 1-2).

## Structure

Obscurin-B (~8 000 aa) comprises ~55 immunoglobulin domains, multiple fibronectin type-III repeats, an IQ motif, an SH3 domain, a tandem RhoGEF-PH module, and C-terminal kinases SK1 and SK2 (marston2017obscurinvariantsand pages 2-4, kontrogiannikonstantopoulos2009musclegiantsmolecular pages 28-29).  
Crystal structures of Drosophila PK1 reveal a canonical bilobal kinase fold with degenerate catalytic motifs and a short regulatory tail, validating its pseudokinase status (zacharchenko2023pk1fromdrosophila pages 11-12).  
Human SK2 retains the VAIK Lys and HRD catalytic triad essential for phosphotransfer, whereas SK1 preserves the VAIK Lys but diverges elsewhere, consistent with differential catalytic output (hu2013thekinasedomains pages 1-2).  
A helix-enriched, intrinsically disordered inter-kinase linker is predicted to act as a mechanosensitive spring coupling the two kinase lobes (zacharchenko2023pk1fromdrosophila pages 7-8).

## Regulation

Autophosphorylation: SK1 phosphorylates seven serines immediately C-terminal to its catalytic domain; mutation of the active-site lysine abolishes these phosphorylation events, confirming cis-autocatalysis (fleming2021exploringobscurinand pages 7-9).  
Phosphorylation of this serine cluster produces discrete Phos-tag mobility shifts (P1–P3) and drives nuclear enrichment of the kinase fragment in differentiated muscle cells (fleming2021exploringobscurinand pages 5-7).  
Multiple ERK consensus sites populate the non-modular COOH-terminus of obscurin-A, indicating potential MAPK regulation (kontrogiannikonstantopoulos2009musclegiantsmolecular pages 28-29).  
Smaller SK1-containing isoforms secreted to the extracellular milieu are modified by N-glycosylation, which correlates with their non-canonical localization (hu2013thekinasedomains pages 1-2).  
Conformational control is additionally mediated by the flexible inter-kinase linker and the minimal regulatory tail of PK1, forming an integrated mechanosensory module (zacharchenko2023pk1fromdrosophila pages 7-8).

## Function

Expression is highest in skeletal and cardiac muscle, with lower levels detected in several non-muscle tissues (randazzo2017thepotentialof pages 6-8, grogan2019unravelingobscurinsin pages 1-2).  
Structural scaffold roles include binding titin Z9/Z10 via Ig58-59, anchoring at Z-discs and M-bands, and interacting with myomesin to stabilize thick-filament organization (kontrogiannikonstantopoulos2009musclegiantsmolecular pages 35-36).  
Obscurin links the sarcoplasmic reticulum to myofibrils through high-affinity binding to sAnk1.5 (armani2006molecularinteractionswith pages 13-13).  
The tandem kinases integrate adhesion and ion-pump regulation: SK2 phosphorylates N-cadherin, while SK1 targets Na⁺/K⁺-ATPase β₁ at intercalated discs (hu2013thekinasedomains pages 1-2, randazzo2017thepotentialof pages 14-16).  
The RhoGEF-PH cassette activates RhoA and RhoQ, promoting myofibril growth and hypertrophic signalling (marston2017obscurinvariantsand pages 2-4).  
Ig58 also binds phospholamban, sequestering it from SERCA2 and thereby modulating Ca²⁺ re-uptake and cardiac rhythmicity (randazzo2017thepotentialof pages 11-14).  
Additional partners include RanBP9, PP2A and dystrophin, positioning obscurin as a hub for cytoskeletal and signalling networks (randazzo2017thepotentialof pages 33-36, manring2017obscurefunctionsthe pages 9-10).

## Other Comments

Pathogenic missense variant R4344Q in Ig58 diminishes titin binding, elevates SERCA2 activity and leads to arrhythmia and hypertrophic cardiomyopathy in knock-in mice and patients (grogan2019unravelingobscurinsin pages 2-4, randazzo2017thepotentialof pages 11-14).  
Missense variants E963K and V2161D co-segregate with familial dilated cardiomyopathy and correspond with reduced obscurin protein abundance (grogan2019unravelingobscurinsin pages 4-5).  
Frameshift mutations clustered near SK1 and adjacent Ig domains are linked to left-ventricular non-compaction cardiomyopathy (grogan2019unravelingobscurinsin pages 4-5).  
Kinase-domain missense W7910R associates with distal muscular dystrophy, underscoring the clinical relevance of SK2 integrity (randazzo2017thepotentialof pages 14-16).  
Multiple truncating alleles produce obscurin haploinsufficiency in explanted dilated cardiomyopathy hearts (marston2015obscnmutationsassociated pages 5-7).

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