## Phylogeny

Protein O-mannose kinase (POMK; SgK196) is an atypical member of the eukaryotic protein kinase superfamily that branches close to the kinome root and is distant from conventional serine/threonine and tyrosine kinase clades (zhu2016structureofprotein pages 1-2). Orthologs with retained catalytic residues are documented in vertebrates such as Mus musculus (81 % identity in the catalytic domain) and Danio rerio (58 % identity), demonstrating strong evolutionary conservation (nagae20173dstructuralanalysis pages 1-2, zhu2016structureofprotein pages 2-3). No fungal or plant orthologs have been reported, underscoring a vertebrate-restricted lineage. Unlike canonical kinases, POMK lacks the classical β3-Lys/αC-Glu ion pair and carries its catalytic Lys in β2, a feature that defines it as a distinct sub-family within the “unclassified/atypical” branch of the kinome (zhu2016structureofprotein pages 2-3).

## Reaction Catalyzed

ATP + GalNAc-β1,3-GlcNAc-β1,4-Man-(Ser/Thr)-α-dystroglycan ⇌ ADP + GalNAc-β1,3-GlcNAc-β1,4-(6-phosphate)-Man-(Ser/Thr)-α-dystroglycan (nagae20173dstructuralanalysis pages 1-2, zhu2016structureofprotein pages 1-2).

## Cofactor Requirements

Catalysis requires divalent cations; crystal structures and in-vitro assays show dependence on Mg²⁺, with Mn²⁺ supporting activity in biochemical assays (zhu2016structureofprotein pages 1-2, unknownauthors2023enzymeassayof pages 1-4).

## Substrate Specificity

POMK exclusively phosphorylates the core M3 trisaccharide GalNAc-β1,3-GlcNAc-β1,4-Man when this glycan is O-linked to α-dystroglycan; the GalNAc-β1,3-GlcNAc disaccharide constitutes the primary recognition determinant (K\_D ≈ 30 µM) (zhu2016structureofprotein pages 6-9, nagae20173dstructuralanalysis pages 1-2). No peptide consensus motif is required, and no activity is detected toward free monosaccharides or unrelated glycans (zhu2016structureofprotein pages 6-9).

## Structure

Type II transmembrane topology: an N-terminal cytosolic tail, a single transmembrane helix, and a luminal kinase domain (residues ~45–349) (nagae20173dstructuralanalysis pages 1-2).  
3D architecture: canonical bilobal fold with a five-stranded β-sheet and αC helix in the N-lobe and a helical C-lobe; solved at 2.1 Å in complex with ADP-AlF₃-Mg²⁺ and substrate analog (zhu2016structureofprotein pages 2-3).  
Catalytic features:  
• Lys91 (β2) coordinates ATP phosphates; it ion-pairs with Asp227 of the activation segment, replacing the classical Lys-Glu pair (zhu2016structureofprotein pages 2-3).  
• Catalytic loop carries an MCD motif; Asp202 acts as the general base (zhu2016structureofprotein pages 3-6).  
• The activation segment begins with a DLD motif; Asp225 chelates the primary Mg²⁺ ion (zhu2016structureofprotein pages 3-6).  
• A disulfide bridge between Cys201 and Cys241 stabilises the active site and orients the substrate (zhu2016structureofprotein pages 3-6).  
• Regulatory spine and hydrophobic spine residues are conserved, supporting an active kinase conformation in the absence of activation-loop phosphorylation (zhu2016structureofprotein pages 3-6).  
Unique elements: active-site migration of catalytic Lys, expanded αE–αF linker accommodating sugar binding groove, and surface pocket that clamps the GalNAc-β1,3-GlcNAc moiety (zhu2016structureofprotein pages 6-9, nagae20173dstructuralanalysis pages 1-2).

## Regulation

Post-translational modifications: three luminal N-glycosylation sequons are present; their occupancy modulates protein folding but regulatory consequences remain undefined (nagae20173dstructuralanalysis pages 1-2).  
Conformational regulation: activity is constitutive; no requirement for activation-segment phosphorylation has been observed (zhu2016structureofprotein pages 3-6).  
No evidence for autophosphorylation, ubiquitination, or allosteric protein partners has been reported.

## Function

Biological role: POMK phosphorylates core M3 on α-dystroglycan in the ER lumen, an obligatory step that permits subsequent ribitol-5-phosphate addition by FKTN/FKRP and LARGE-mediated polymerisation of full-length matriglycan, thereby enabling high-affinity binding of laminin-G domain ECM proteins (walimbe2020pomkregulatesdystroglycan pages 1-2, nagae20173dstructuralanalysis pages 1-2).  
Expression: high in fetal brain, skeletal muscle, heart and kidney, with lower yet significant levels in adult cerebrum, hippocampus and skeletal muscle (costanzo2014pomkmutationsdisrupt pages 4-6).  
Pathway context: functions downstream of POMGNT2 and B3GALNT2 and upstream of FKTN, FKRP and LARGE within the matriglycan synthesis cascade (walimbe2020pomkregulatesdystroglycan pages 2-4).  
Interactors/substrates: direct substrate is α-dystroglycan; indirect functional coupling to LARGE1 is demonstrated by preferential LARGE1 binding to phosphorylated core M3 (walimbe2020pomkregulatesdystroglycan pages 2-4).  
Physiological impact: loss of POMK results in truncated matriglycan, reduced laminin binding, sarcolemmal instability, impaired muscle force and neuronal migration defects (walimbe2021proteinomannosekinasemediated pages 163-168, costanzo2014pomkmutationsdisrupt pages 1-2). POMK activity also modulates susceptibility of α-dystroglycan to Lassa virus engagement (zhu2016structureofprotein pages 1-2).

## Other Comments

Disease associations: recessive mutations cause the dystroglycanopathy spectrum, including Walker–Warburg syndrome, muscle-eye-brain disease and limb-girdle muscular dystrophy (zhu2016structureofprotein pages 9-11, costanzo2014pomkmutationsdisrupt pages 1-2).  
Notable missense mutations: D204N abolishes catalysis; K93A, D227A and A230E disrupt substrate positioning; C201S or C241S break the stabilising disulfide, all leading to loss of α-dystroglycan phosphorylation and reduced laminin binding (zhu2016structureofprotein pages 9-11, walimbe2020pomkregulatesdystroglycan pages 2-4).  
Phenotypic variability: complete POMK loss yields milder clinical courses than defects in downstream enzymes, correlating with residual synthesis of short matriglycan that retains partial ECM binding (walimbe2021proteinomannosekinasemediated pages 111-115).

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