## Phylogeny

MYO3A belongs to class III myosins, a highly divergent branch of the myosin superfamily first described in Drosophila as the NINAC protein (Dosé et al., 2007; Komaba et al., 2003). Its N-terminal kinase domain is related to HGK-family members (HPK, GCK) and is grouped within the p21-activated kinase (PAK) superfamily of serine/threonine kinases (Coluccio, 2008).

## Reaction catalysed

ATP + [protein]-L-serine ⇌ ADP + [protein]-L-serine phosphate  
ATP + [protein]-L-threonine ⇌ ADP + [protein]-L-threonine phosphate  
ATP + H₂O ⇌ ADP + phosphate  
(Coluccio, 2008)

## Cofactor requirements

ATP is required for both kinase and motor activities; Mg²⁺ supports the motor ATPase reaction. Calmodulin (Ca²⁺-binding light chain) binds the two IQ motifs and modulates motor function (Dosé et al., 2007; Komaba et al., 2010).

## Substrate specificity

MYO3A is a serine/threonine kinase that phosphorylates its own regulatory light chain, calponin, actin, and myelin basic protein in vitro (Coluccio, 2008). Positional scanning peptide array analysis defined a detailed position-specific scoring matrix and optimal consensus motif for human MYO3A (Johnson et al., 2023).

## Structure

The monomeric protein comprises:  
• N-terminal kinase domain with a conserved glycine-rich loop and catalytic Lys (Komaba et al., 2003).  
• Myosin motor domain that binds actin and hydrolyses ATP (Coluccio, 2008).  
• Neck region containing two IQ motifs for calmodulin binding (Dosé et al., 2007).  
• C-terminal tail harbouring an additional actin-binding site; a MORN4-binding segment has been crystallised (PDB 6JLE) (Li et al., 2019).

## Regulation

Autophosphorylation by the kinase domain increases kinase activity ≈3.3-fold (Coluccio, 2008). Phosphorylation of residues in or near loop 2 of the motor domain elevates ATPase rate, lowers actin affinity, and reduces duty ratio, thereby attenuating processivity (Komaba et al., 2010). Protein kinase C can further phosphorylate sites in the tail (Coluccio, 2008).

## Function

MYO3A is highly expressed in sensory cells, localising to stereocilia tips of cochlear hair cells and to calycal processes of retinal photoreceptors (Grati et al., 2016; Raval et al., 2016). Acting as a plus-end directed motor, it transports cargoes—including espin-1, espin-like, and PCDH15-CD2—along actin filaments to protrusion tips (Dantas et al., 2018; Grati et al., 2016). This trafficking maintains stereocilia length and staircase organisation essential for hearing (Dantas et al., 2018; Maekawa et al., 2025). The interaction with espin-1 is required for its “inchworm-like” motility (Miyoshi et al., 2024). Functional redundancy with paralog MYO3B may occur in photoreceptors (Miyoshi et al., 2024).

## Other comments

Pathogenic MYO3A variants cause autosomal recessive DFNB30 and autosomal dominant late-onset hearing loss. Documented mutations include p.Gly488Glu, p.Leu697Trp, and p.Ser614Phe, each impairing enzymatic or motor properties and disrupting stereocilia maintenance (Dantas et al., 2018; Grati et al., 2016).

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