

**Table S1. Myosin-I structure, function, localization, tissue expression and associated diseases for each isoform.**

Isoform	# of IQ in LCBD	Domains in Tail	Intracellular Localization and Proposed Functions	High Tissue Expression	Associated Diseases
<b>Myosin-Ia*</b>	3 (Swanljung-Collins and Collins, 1991)	PH domain (Hokanson et al., 2006; Tyska and Mooseker, 2002)	<ul style="list-style-type: none"> <li>Binds PtdIns(4,5)P<sub>2</sub> and anionic phospholipids (Hayden et al., 1990); membrane binding supplemented by IQ-region binding (Swanljung-Collins and Collins, 1994)</li> <li>Motility (gliding filament assay) (Collins et al., 1990) and ATPase (Fanning et al., 1994) inhibited by nonmuscle tropomyosin-coated actin filaments</li> <li>Localizes to Golgi-derived vesicles (Fath and Burgess, 1993; Fath et al., 1994)</li> <li>Localizes to intestinal brush border, where it is essential for microvillar structure and organization; involved in membrane tension and apical membrane vesicle shedding from microvillus tip (McConnell and Tyska, 2007; Tyska et al., 2005)</li> </ul>	Small intestines, colon (Skowron et al., 1998)	Non-syndromic and autosomal dominant hearing loss (Donaudy et al., 2003)
<b>Myosin-Ib</b>  Post-power-stroke motor domain	4-6* (Lin et al., 2005; Ruppert et al., 1993; Sherr et al., 1993)	PH domain (Hokanson et al., 2006)	<ul style="list-style-type: none"> <li>Binds PtdIns(4,5)P<sub>2</sub>, PtdIns(3,4,5)P<sub>3</sub>, and anionic phospholipids (Komaba and Coluccio, 2010)</li> <li>Not found on nonmuscle tropomyosin actin filaments (Tang and Ostap, 2001)</li> <li>Localizes to Arp2/3-nucleated actin filaments (Almeida et al., 2011)</li> <li>Localizes to endosomes and lysosomes (Cordonnier et al., 2001; Raposo et al., 1999)</li> <li>Influences transport from trans-Golgi network to endosomes; involved in tubulation (Almeida et al., 2011)</li> <li>Found in cytosol, on the plasma membrane and endoplasmic reticulum-like microsomes, Golgi (Balish et al., 1999)</li> <li>Found on lamellipodia, membrane ruffles, and filopodia (Komaba and Coluccio, 2010; Lewis and Bridgman, 1996; Prospéri et al., 2015; Ruppert et al., 1995; Tang and Ostap, 2001)</li> <li>Localizes to multi-vesicular bodies (Salas-Cortes et al., 2005)</li> <li>Localizes to kidney cell brush border apical membrane and</li> </ul>	Lung, liver, heart, brain, and most everywhere else (Ruppert et al., 1993; Sherr et al., 1993, 19)	Lymph node metastasis of human head and neck squamous cell carcinoma (Ohmura et al., 2015)

structure (PDB:4L7 9(Shuman et al., 2014))			<ul style="list-style-type: none"> <li>stabilizes amino acid transporters (Komaba and Coluccio, 2015)</li> <li>Involved in Pmel17 sorting into melanosomes (Salas-Cortes et al., 2005)</li> <li>Effector of EphB2 signaling to control cell repulsion (Prospéri et al., 2015)</li> <li>Localizes to lamellar bodies of Alveolar type II cells: involved in tethering lamellar body and/or slowing actin coat compression during exocytosis of surfactants (Kittelberger et al., 2016)</li> </ul>		
<b>Myosin- Ic*</b>	3 (Mancev a et al., 2007; Sielski et al., 2014)	PH domain (Hokanson et al., 2006)	<ul style="list-style-type: none"> <li>Binds PtdIns(4,5)P<sub>2</sub> (Hokanson and Ostap, 2006; Hokanson et al., 2006), supplemented by anionic phospholipids (McKenna and Ostap, 2009)</li> <li>Not found on nonmuscle tropomyosin actin filaments (Kee et al., 2015; McIntosh et al., 2015)</li> <li>Functions in GLUT4 cargo docking and transport beneath the plasma membrane (Boguslavsky et al., 2012; Bose et al., 2002; Bose et al., 2004; Chen et al., 2007; Huang et al., 2005; Toyoda et al., 2011; Yip et al., 2008)</li> <li>Involved in lipid raft recycling tubule deformation and transport (Brandstaetter et al., 2012), and found in lipid rafts in the plasma membrane; this also affects cell spreading, migration, and <i>Salmonella</i> invasion (Maravillas-Montero et al., 2011); cholesterol trafficking affects lysosome-autophagosome fusion (Brandstaetter et al., 2014)</li> <li>Localizes to podocyte membrane where it is involved in transport of Neph1 to podocyte membrane (Arif et al., 2011); Involved in regulation of Na<sup>+</sup> channel after ADH stimulation of collecting ducts (Wagner et al., 2005)</li> <li>Localizes to plasma membrane: mediates cell adhesion and spreading, stabilizes E-cadherin adherens junctions (Balish et al., 1999; Fan et al., 2012; Oh et al., 2013; Sokac and Bement, 2000; Tokuo and Coluccio, 2013)</li> <li>Localizes to lamellar bodies of Alveolar type II cells: involved in actin coat compression during exocytosis of surfactants (Kittelberger et al., 2016)</li> </ul>	Kidney, muscle, adipose, small intestine (Skowron et al., 1998; Tyska et al., 2005) and most everywhere else	Kidney disease (Arif et al., 2011; Wagner et al., 2005) and deafness (Batters et al., 2004; Holt et al., 2002)

LCBD and TH2 structure (PDB:4R8G (Lu et al., 2015))			<ul style="list-style-type: none"> <li>Facilitates G-actin transport to the leading edge of migrating epithelial cells by binding G-actin and possibly facilitating plasma membrane ruffling (Fan et al., 2012)</li> <li>Involved in IKK transport toward plasma membrane, mediating TNF-<math>\alpha</math>-induced downregulation of IRS-1 and glucose uptake (Nakamori et al., 2006)</li> <li>Involved in VEGF2 delivery to plasma membrane (Tiwari et al., 2013)</li> <li>Promotes ER sheet stabilization over reticular formation (Joensuu et al., 2014)</li> <li>Involved in B-cell cytoskeletal rearrangements at the immunological synapse; contributes to antigen presentation (Maravillas-Montero et al., 2011)</li> <li>Involved in neuronal growth cone cytoskeletal rearrangement, membrane protrusion, and compensatory endocytosis (Sokac et al., 2006; Wang et al., 2003)</li> <li>Involved in inner ear mechanical adaptation (Batters et al., 2004; Gillespie et al., 1993; Holt et al., 2002)</li> <li>Participates in establishment of left-right asymmetry during <i>Drosophila</i> development (Hozumi et al., 2006; Okumura et al., 2015; Petzoldt et al., 2012; Spéder et al., 2006)</li> <li>One splice isoform localizes to the nucleus: interacts with RNA polymerase I and II, may be involved in transcription and in helping direct long-range chromosomal movement (Chuang et al., 2006; Kyselá et al., 2005; Percipalle et al., 2006; Pestic-Dragovich et al., 2000; Philimonenko et al., 2004)</li> </ul>		
<b>Myosin-Id*</b>	2 (Bähler et al., 1994; Köhler et al., 2005)	PH domain (Hokanson et al., 2006)	<ul style="list-style-type: none"> <li>Both TH1 and IQ regions are needed for appropriate cellular targeting (Benesh et al., 2010)</li> <li>Localizes to intestinal brush border microvilli tips and basolateral membrane (Benesh et al., 2010)</li> <li>Involved in fusion of early endosomes (from apical or basolateral membrane) with recycling endosomes (Huber et al., 2000)</li> <li>Involved in plasma membrane tension (Nambiar et al., 2009)</li> <li>Myo31DF participates in establishment of left-right asymmetry</li> </ul>	Brain (CNS and PNS) (Bähler et al., 1994; Benesh et al., 2012; Cahoy et al., 2008; Nielsen et al., 2006; Sherr et al., 1993), liver, and small	Autism (Stone et al., 2007)

			<p>during <i>Drosophila</i> development through interactions with <math>\beta</math>-catenin and DE-cadherin at adherens junctions; antagonized by Myo61F (Hozumi et al., 2006; Okumura et al., 2015; Petzoldt et al., 2012; Spéder et al., 2006)</p> <ul style="list-style-type: none"> <li>Involved in planar cell polarity of ciliated tracheal epithelial cells (Hegan et al., 2015)</li> </ul>	intestines (Bähler et al., 1994; Benesh et al., 2010)	
<b>Myosin-Ie</b>	1 (Stöffler and Bähler, 1998)	PH domain, TH2, and SH3 domain (Berg et al., 2001; Hokanson et al., 2006; Stöffler and Bähler, 1998)	<ul style="list-style-type: none"> <li>Localizes to the plasma membrane</li> <li>Found at cell-cell contacts and adherens junctions (Bi et al., 2013; Stöffler et al., 1995; Stoffler et al., 1998, 3)</li> <li>Involved in regulated secretion (Schietroma et al., 2007), clathrin-mediated endocytosis (Cheng et al., 2012; Feeser et al., 2010; Krendel et al., 2007), and phagosome closure (Diakonova et al., 2002; Swanson et al., 1999),</li> <li>Involved in lamellipodial dynamics and adhesion formation (Gupta et al., 2013)</li> <li>Contributes to regulation of invadosome structure and dynamics (Ouderkirk and Krendel, 2014)</li> <li>Regulates TLR4-triggered macrophage spreading and antigen presentation (Wenzel et al., 2015)</li> </ul>	Immune cells (B-cells, lymph, lung, spleen, NK, macrophages, dendritic cells) (Diakonova et al., 2002; Kim et al., 2006; Wenzel et al., 2015), small intestine (Tyska et al., 2005), kidney podocytes (Bi et al., 2013; Krendel et al., 2009; Mele et al., 2011), and most other cells	Kidney disease (Bi et al., 2013; Krendel et al., 2009; Mele et al., 2011), and associated with tryglycerides in GWAS for arteriosclerosis (Inouye et al., 2012)
<b>Myosin-If</b>	1 (McConnell and Tyska, 2010)	PH domain, TH2, and SH3 domain (Berg et al., 2001; Hokanson et al., 2006)	<ul style="list-style-type: none"> <li>Localizes to plasma membrane</li> <li>Modulates adhesion to extracellular environment by preventing excessive exocytosis and inappropriate cell spreading (not due to loss of cortical tension) in <math>\beta</math>2-integrin-mediated interactions (Kim et al., 2006)</li> </ul>	Neutrophils, spleen, lymph nodes, thymus, and lung (Kim et al., 2006)	Acute monocytic leukemia (Taki et al., 2005) and non-syndromic deafness (Baek et al., 2012; Chen et al., 2001)

<b>Myosin-Ig</b>	2 (Patino-Lopez et al., 2010)	PH domain (Hokanson et al., 2006; Patino-Lopez et al., 2010)	<ul style="list-style-type: none"> <li>Binds PtdIns(4,5)P<sub>2</sub> and PtdIns(3,4,5)P<sub>3</sub> (Dart et al., 2012; Patino-Lopez et al., 2010)</li> <li>Localizes to plasma membrane (Hao et al., 2008; Nebl et al., 2002)</li> <li>Generates membrane tension (and maintains elasticity) important for T cell migration, enhances T cell-dendritic cell interactions during lymph node surveillance (Gérard et al., 2014; Olety et al., 2010)</li> <li>Involved in generating/maintaining cortical tension in B-cells, affecting cell adhesion, spreading, phagocytosis, and endocytosis (López-Ortega et al., 2016)</li> <li>Involved in phagosome closure (Dart et al., 2012)</li> </ul>	Hematopoietic cells (thymus, lymph, spleen), neutrophils, T-cells, and pre-B-cells (Hao et al., 2008; Nebl et al., 2002; Olety et al., 2010)	
<b>Myosin-Ih</b>	2 (McConnell and Tyska, 2010)	PH domain (Hokanson et al., 2006)	<ul style="list-style-type: none"> <li>No known functions/localizations</li> </ul>	Testis, adipocytes, heart, and neutrophils (Fishilevich et al.)	Marker for mandibular prognathism phenotype (Tassopoulou-Fishell et al., 2012)

(\*) Indicates alternative splicing of motor or light-chain-binding domains. LCBD, light-chain-binding domain; PH, pleckstrin homology.