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Review: Cytoplasmic dynein motors in photoreceptors

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Cytoplasmic dyneins (dynein-1 and dynein-2) transport cargo toward the minus end of microtubules and thus, are termed the "retrograde" cellular motor. Dynein-1 cargo may include nuclei, mitochondria, membrane vesicles, lysosomes, phagosomes, and other organelles. For example, dynein-1 works in the cell body of eukaryotes to move cargo toward the microtubule minus end and positions the Golgi complex. Dynein-1 also participates in the movement of chromosomes and the positioning of mitotic spindles during cell division. In contrast, dynein-2 is present almost exclusively within cilia where it participates in retrograde intraflagellar transport (IFT) along the axoneme to return kinesin-2 subunits, BBSome, and IFT particles to the cell body. Cytoplasmic dyneins are hefty 1.5 MDa complexes comprised of dimers of heavy, intermediate, light intermediate, and light chains. Missense mutations of human *DYNC1H1* are associated with malformations of cortical development (MCD) or spinal muscular atrophy with lower extremity predominance (SMA-LED). Missense mutations in *DYNC2H1* are causative of short-rib polydactyly syndrome type III and nonsyndromic retinitis pigmentosa. We review mutations of the two dynein heavy chains and their effect on postnatal retina development and discuss consequences of deletion of *DYNC1H1* in the mouse retina.

Cytoplasmic dyneins from yeast to human have been studied intensively, focusing on cell division or organelle movement in vivo and in vitro. Dynein-1 and dynactin form a large multimeric (>2 MDa) complex which is expressed ubiquitously, whereas the more specialized dynein-2 is expressed prominently in ciliated cells to enable ciliogenesis. Individual dynein-1 subunits are responsible for cargo attachment, interaction between dynein and dynactin, and processivity along microtubule tracks. During embryonic development, dynein plays a crucial role in mitotic cell division, the orientation and assembly of the bipolar spindle, nuclear migration, chromosome segregation, and cytokinesis [1,2] (see review by [3,4]). In postmitotic neurons, dynein moves cargo over long distances toward the minus end of microtubules and is responsible for neuronal survival [5]. The complexity of subunit interaction and the effect of various mutations in heavy chains and subunits is astonishing and just beginning to be understood. Much has been achieved since the discovery of dynein (named after "dyne" meaning force) in *Tetrahymena* (presumably dynein-2) [6], cytoplasmic dynein in *Caenorhabditis elegans* [7], molecular cloning of bovine DYNC1H1 [8], and the discovery of dynactin (dynein activator) [9]. Although cryoelectron microscopy has solved structural queries of the MDa complexes, the nature of cargo adaptors, details of cargo attachment or unloading, and transition from inhibited to active states remain largely unknown. We provide a short review of cytoplasmic dynein subunits compiled from abundant dynein literature and then focus on the dynein heavy chains and mutations linked to disease. Finally, we discuss effects of heavy chain mutations on mouse and zebrafish photoreceptor protein transport.

The dynein superfamily: The dynein superfamily is divided into two main categories: (a) axonemal and (b) cytoplasmic dyneins (see recent reviews [10,11]). Axonemal dyneins, present in motile cilia and flagella, power ciliary and flagellar beating by producing sliding movements between adjacent outer-doublet microtubules in organisms such as *Chlamydomonas* [12,13]. Cytoplasmic dyneins, distantly related to axonemal dyneins [14], are further subdivided into intracellular dyneins (dynein-1) and intraflagellar transport (IFT) dyneins (dynein-2). As the main retrograde motor of eukaryotic cells, dynein-1 regulates the formation of mitotic spindles during cell division and moves cargo toward microtubular minus ends [15]. In neurons where the cell body can be hundreds of microns distant from peripheral synapses, vesicular transport is essential for survival. Dynein-2 is present almost exclusively within cilia (or the photoreceptor outer segments) where it participates in retrograde IFT along the axoneme [16-18]. Dynein-2 enters primary cilia as cargo of an anterograde IFT train powered by kinesin-2 [19] and transports kinesin-2 subunits, BBSome, and IFT particles in

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Table 1. Subunits of dynein-1 and dynein-2.

Protein	Name	Gene	OMIM	AA
DHC1	Dynein heavy chain	*DYNC1H1*	600112	4646
DIC1	Dynein intermediate chain 1	*DYNC1I1*	603772	645
DIC2	Dynein intermediate chain 2	*DYNC1I2*	603331	638
DLIC1	Dynein light intermediate chain 1	*DYNC1LI1*	615890	523
DLIC2	Dynein light intermediate chain 2	*DYNC1LI2*	617083	492
LC8-1	**Dynein light chain LC8-type 1**	***DYNLL1***	**601562**	**89**
LC8-2	**Dynein light chain LC8-type 2**	***DYNLL2***	**608942**	**89**
ROBL1	**Dynein light chain roadblock 1**	***DYNLRB1***	**607167**	**96**
ROBL2	**Dynein light chain roadblock 2**	***DYNLRB2***	**607168**	**96**
TCTEX1	**Dynein light chain Tctex-type 1**	***DYNLT1***	**601554**	**113**
TCTEX2	**Dynein light chain Tctex type 2**	***DYNLT2***	**186977**	**198**
TCTEX3	**Dynein light chain Tctex-type 3**	***DYNLT3***	**300302**	**116**
DHC2	Dynein 2 heavy chain 1	*DYNC2H1*	603297	4314
DIC6	Dynein 2 intermediate chain 1 WDR60	*DYNC2I1*	615462	1066
DIC5	Dynein 2 intermediate chain 2 WDR34	*DYNC2I2*	615463	536
D2LIC	Dynein 2 light intermediate chain 1	*DYNC2LI1*	617083	352
TCTEX1D2	dynein light chain Tctex-type 2B	*DYNLT2B*	617353	142

Column 1, non-standard subunit designations; column 2, official gene nomenclature (HGNC); column 3, gene symbol; column 4, number of amino acids. Bold-faced subunits are shared between dynein-1 and dynein-2.

a retrograde direction to the cell body [20,21]. Dynein-2 also participates in organizing the transition zone [22,23].

Dynein subunits and structure: Dynein-1 exists in an inhibited, weakly processive state (the φ (phi) particle) [24] which is activated by binding to dynactin and an effector, such as bicaudal D homolog 2 (BICD2) or HOOK3 [25,26], reviewed by [27]. The 1.5 MDa dynein complex is composed of a pair of force-generating heavy chains (DYNC1H1) and a set of accessory components termed intermediate, light intermediate, and light chains (Table 1). The heavy chain serves as a scaffold organizing the distribution of dynein subunits and is subdivided into an N-terminal tail and a C-terminal motor domain (Figure 1A) [28,29]. The dynein-1 tail domain 3-D structure is formed by a homodimer of DYNC1H1 bound together at a 200-amino acid N-terminal dimerization domain [30]. Each copy of DYNC1H1 binds to a dynein intermediate chain (DIC1 or DIC2) and a light intermediate chain (DLIC1 or DLIC2), resulting in the overall dynein-1 complex containing DIC and DLIC homodimers. Each DIC has three dynein light chains (roadblock or ROBL (DYNLRB), LC8 (DYNLL1/2), and TCTEX (DYNLT1–3) which bind to the extended DIC N-terminus forming a dimer with the light chain bound to the neighboring DIC (Figure 1C) [30]. The dynein-1 complex tail also links its two motor domains to dynactin and cargo adaptors with light chains believed to be involved in dynein complex assembly, stability, motor–cargo interactions, and motor activity regulation [31].

The dynein-2 heavy chain, DYNC2H1, is closely related to that of dynein-1 (Figure 1B). An amino acid pairwise alignment of human DYNC1H1 and DYNC2H1 chains (generated with Clustal-EMBL) shows 46% similarity and 27% identity. Dynein-2 contains the heavy chain DYNC2H1, intermediate chains *WDR34* and *WDR60*, light intermediate chain D2LIC (*DYNC2LI1*), and light chain *TCTEX1D2* [21,32] (Table 1). *ROBL1/2*, *LC81/2*, and *TCTEX1–3* subunits (bold-faced in Table 1) are shared by dynein-1 and dynein-2. The dynein-2 3-D structure was recently determined with cryoelectron microscopy (Cryo-EM) [33]. DYNC2H1 forms a homodimer in which one copy of the DYNC2H1 tail region is straight, while the other assumes a zig-zag conformation (Figure 1D). Both copies of DYNC2H1 bind a light intermediate chain DYNC2LI1. Two intermediate chains, WDR60 and WDR34, form a heterodimer that binds and stabilizes DYNC2H1. The N-proximal regions are held together by an array of light chains consisting of one ROBL dimer and three LC8 dimers. The structural organization consists of DYNC2H1–DYNC2LI1 and WDR60–WDR34–ROBL–LC8–TCTEX–TCTEX1D2 subcomplexes (Figure 1D) [33].

Each dynein motor is built around a ring of six ATPases associated with various activities (AAA+) of the heavy chain

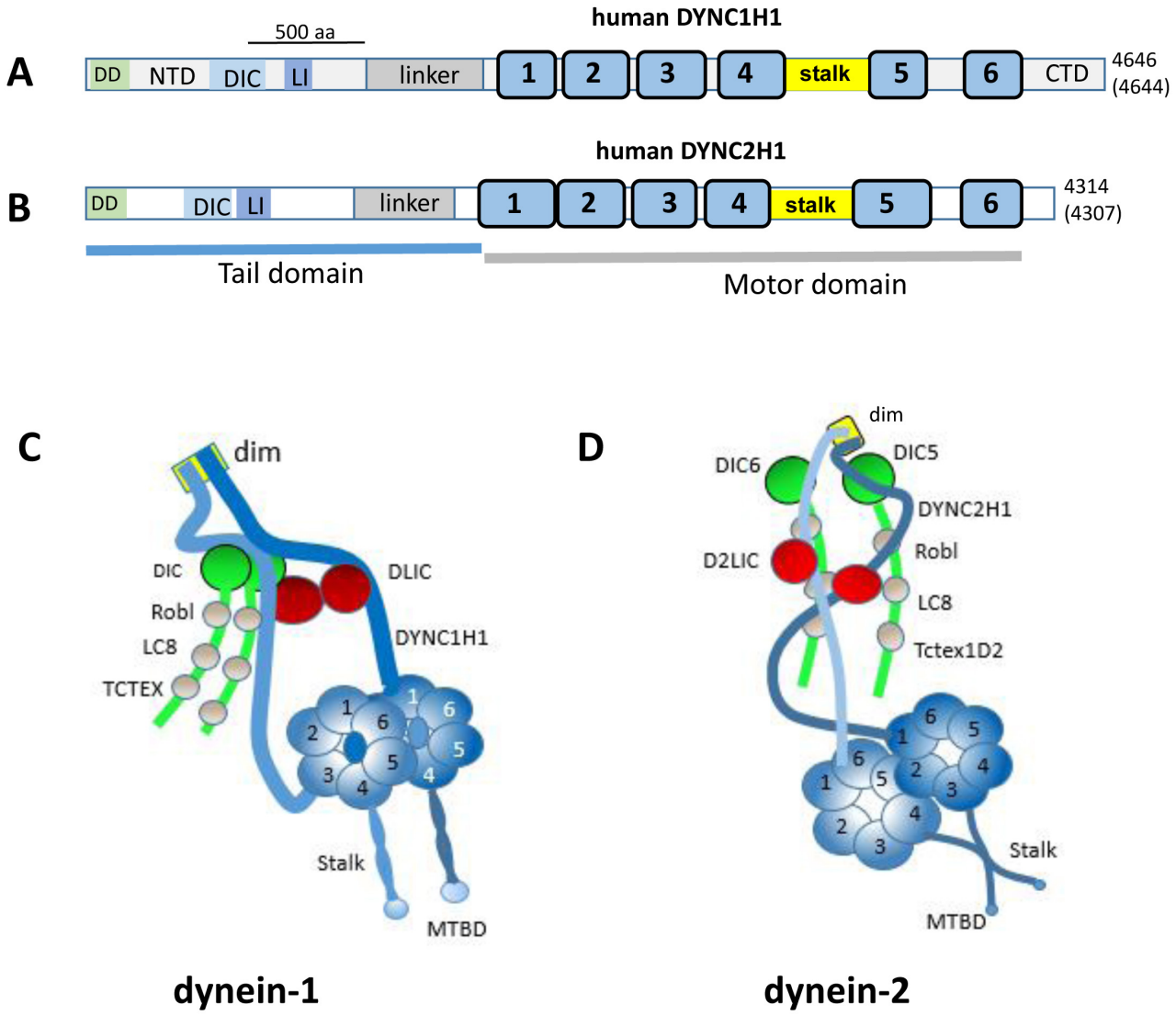

Figure 1. Human dynein-1 and dynein-2. **A, B**: Schematic representation of human dynein heavy chain DYNC1H1 (**A**) and DYNC2H1 (**B**) domain structures. DD, dimerization domain; NTD, N-terminal domain; DIC, dynein intermediate chain interaction site; LI, light intermediate interaction site; blue bars, ATPase domains 1–6; stalk; MBD, microtubule-binding domain; CTD, C-terminal domain. Numbers at the C-terminus indicate amino acids in the human and mouse, with those of the mouse enclosed by parentheses. Adapted from [88] and [59]. The 500 aa bar indicates the length occupied by 500 amino acids. **C, D**: representations of multimeric dynein-1 and dynein-2. The heavy chains form homodimers, the scaffolds of which organize the distributions of intermediate, light intermediate, and light chains (adapted from [45] and [33]. The N-terminal 200 amino acids represent the dimerization domain (dim).

(Figure 1C, D). The microtubule-binding domain sits at the tip of a coiled-coiled stalk emerging from AAA4. To move along the microtubule track, the motor domain couples ATP hydrolysis with a mechanochemical cycle (reviewed in [10,34]). Briefly, in the ADP state, the stalk is bound to microtubules. Binding of ATP to AAA1 releases the stalk from the microtubules which induces a bend in the linker. The stalk swings to a new site, and hydrolysis of ATP causes rebinding to the microtubule followed by straightening of the linker (powerstroke), and the next cycles begin. X-ray crystallography and high-resolution cryo-EM have provided exquisite insights into how the dynein/dynactin supercomplex moves along microtubules, but the precise molecular

mechanisms responsible for dynein motility on microtubules remain largely unknown [10].

Dynactin, a dynein-1 cofactor: Adaptor (or effector) proteins recruit dynein-1 to the essential motor dynactin complex. Dynactin (1 MDa) is a heteromultimeric complex consisting of 23 polypeptides (11 different proteins) and acts as a dynein-1 cofactor. Dynactin and a cargo adaptor are essential for cytoplasmic dynein to move membrane vesicles along microtubules [35]. Dynactin consists of three major structural domains: the sidearm shoulder, the Arp1 filament, and the pointed end complex (Figure 2A). The sidearm shoulder contains p150^{Glued} (DCTN1) with an N-terminal microtubule-binding domain, p50/dynamitin (DCTN2), and p24/p22 subunits (DCTN3). The ARP1 filament consists of ARP1 (ACTR1A), actin, and CapZ. The pointed end complex contains ARP11, p62 (DCTN4), p25 (DCTN5), and p27 (DCTN6). The chain lengths vary from approximately 200 to 1,200 amino acids (Table 2).

Dynein-1 and dynactin interact directly through the binding of dynein intermediate chains (DICs) with p150^{Glued}, but the interaction is weak (Figure 2B). Dynein and dynactin can be induced to form a tight complex in the presence of cargo adaptors such as BICD2, HOOK1–5, or Spindly which activate cytoplasmic dynein to move for long distances along microtubules [26,34,36,37]. In contrast to dynein-1, dynein-2 does not employ dynactin to function as a motor [32,33].

How do dynein and dynactin transport cargo?: Dynein may transport multiple cargos, likely through the use of different cargo adaptors [27,38]. Adaptor proteins have been identified that mediate specific cargo transport in cultured cells. Cargo specificity and processivity depend on the interaction of dynein-1 with its dynactin complex, and a series of cargo-specific effectors, including BICD2 [34,39], Hook1–3 [38,40,41], Spindly [42], FIP3 [43], and Ninein/ninein-like (NIN/NINL) [44]. These proteins are unrelated by sequence, associate with different cargos, contain large portions of predicted coiled-coil structures, and interact with dynein-1 and dynactin to activate processive motility. BICD2 is a coiled-coil homodimer which has been shown to link Golgi-derived vesicles to dynein-1 in several cell lines [34,39]. The BICD2 N-terminal enables association of dynactin and dynein to form a tight complex [34]. Hook1 is an 80 kDa protein with an N-terminal DLIC1 and a C-terminal cargo binding domain [44]. These cargo adaptors are multifunctional proteins that can bind to the protein on a membranous cargo vesicle [38]. Hook3, a cargo adaptor involved in Golgi and endosome transport, forms a motile dynein-1/dynactin complex by interacting directly with DLIC1. Dynein mobility is impaired if Hook3 cannot bind [38]. All known dynein adaptor activators, including BICD2 and HOOK3, interact directly with DLICs. A DLIC anchors to the heavy chain through multiple domain interactions, and its C-terminal helices bind to the activating adaptors [44]. A schematic model depicting dynein-1/dynactin, a cargo adaptor, and its cargo is shown (Figure 2B).

Dynein heavy chain mutations—Mutations in the human *DYNC1H1* gene (Figure 3) cause a wide array of neurodegenerative disease, e.g., spinal muscular atrophy with lower extremity dominance (SMA-LED), congenital muscular dystrophy (CMD), Charcot-Marie-Tooth disease (CMT), and intellectual disability (reviewed in [45]). More than 30 single point mutations in *DYNC1H1* are known to associate with dyneinopathies [46-48], many of which cause malformations of cortical development (MCD; mutations shown in black typeface, Figure 3A). A H306R mutation is associated with autosomal dominant Charcot-Marie-Tooth disease type 2O (CMT2O), causing abnormal gait and falls associated with distal lower limb weakness [49]. Human E1518K and H3822P missense mutations in *DYNC1H1* are each causative of mental retardation [50–52] (red mutations, Figure 3A). Numerous mutations in *DYNC1H1* were found to be causative of SMA-LED [51,53] (blue mutations, Figure 3A). A G3658 mutation in AAA5 of human *DYNC1H1* was associated with MCD and cataract, suggesting a possible role in human ocular development [54]. Using budding yeast as a model organism for dynein dysfunction, 17 single point mutations associated with human disease were analyzed [55]. Spindle tracking in live cells, single molecule mobility assays, localization, and structural assessments showed that tail mutations associated with SMA-LED are less severe relative to MCD motor mutations which strongly affect spindle positioning, localization, and velocity [55].

Various missense mutations of *DYNC2H1* in humans are associated with short-rib thoracic dysplasia 3 (SRTD3), with or without polydactyly, a group of autosomal recessive ciliopathies characterized by a constricted thoracic cage, short ribs, and shortened tubular bones (Figure 3B) [56–58]. The human *DYNC2H1* gene produces two splice variants (isoforms 1 and 2) which differ in the presence of a miniexon (exon 64) of seven amino acids (IIGLKSW; Figure 3C). Isoform 2 is predominant in the human retina [59]. The miniexon of isoform 2 consisting of seven amino acids (IIGLKSW) is located at the fifth AAA+ module of the DYNC2H1 motor domain. A null mutation (pSer3279*) in the miniexon of human isoform 2 was found to be associated with nonsyndromic retinitis pigmentosa (RP) [59]. The stop codon truncates DYNC2H1 after residue 3278. The DYNC2H1 RP phenotype typically presents with constricted visual field,

reduced visual acuity, and attenuated electroretinography (ERG) responses.

Mouse Dync1h1 mutants and phenotypes—Three mouse mutants, "legs at odd angles" (*Loa*), "Cramping 1" (*Cra1*), and "Sprawling" (*Swl*), display autosomal dominant mouse phenotypes that arose from either ENU mutagenesis or radiation generating missense mutations in the *Dync1h1* tail domain (Figure 3A). The *Loa* and *Cra1* mutations consist of a F580Y or Y1055C mutation, respectively, in the *DYNC1H1* N-terminal region [60,61]. *Cra1*/+ mice exhibit early-onset stable behavioral deficits, including abnormal hind limb posturing and decreased grip strength [62]. *Loa*/+ mice exhibit defects in retrograde axonal transport [60] and

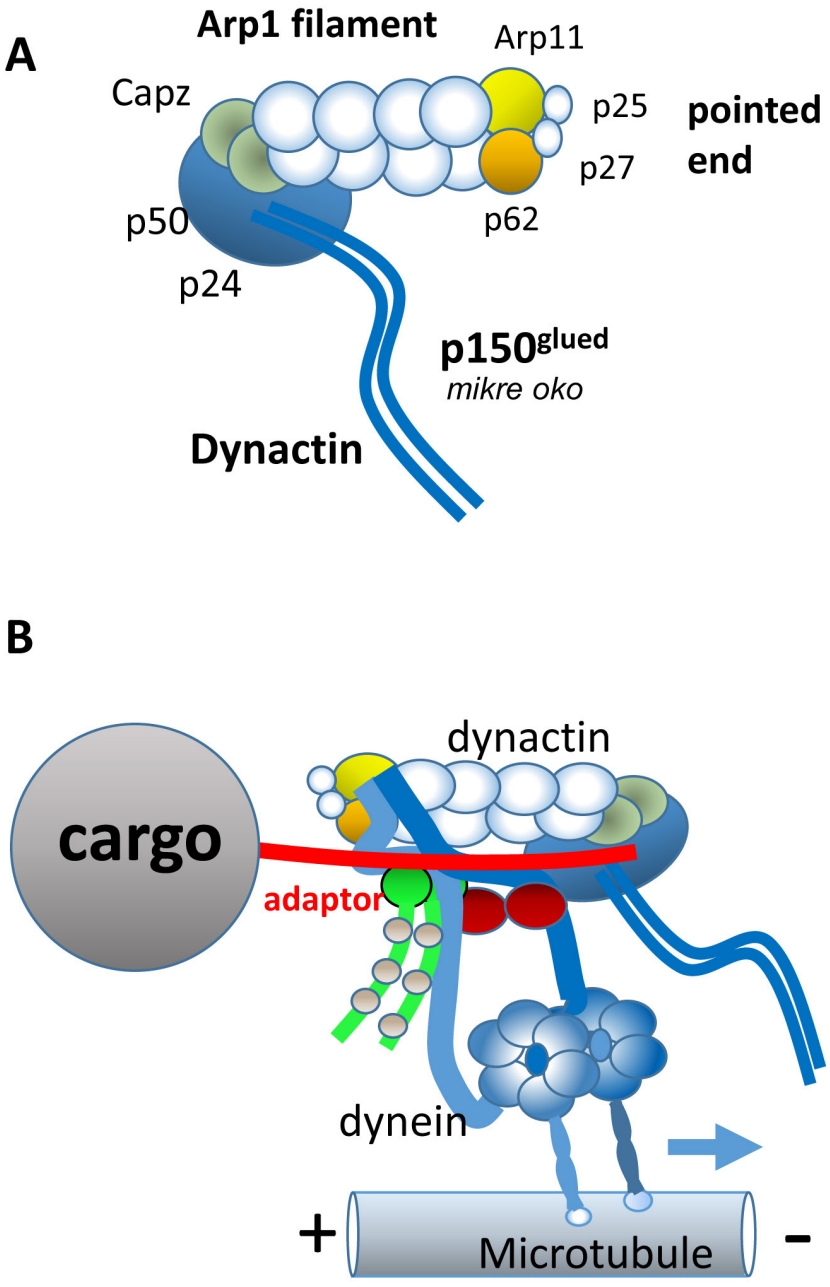

Figure 2. Dynactin and dynein/dynactin complex. **A**: Schematic representation of dynactin (adapted from [27]. **B**: Dynein-1 in complex with dynactin. The adaptor (red) contains multiple coiled-coil domains attaching dynein-1 via DLIC to dynactin, generating an active molecular motor moving toward the microtubule minus end.

Table 2. Subunits of dynactin.

Protein	Name	Gene	OMIM	AA
p150^{Glued}	dynactin subunit 1	*DCTN1*	601143	1278
p50/dynamitin	dynactin subunit 2	*DCTN2*	607376	406
p22 /24	dynactin subunit 3	*DCTN3*	607387	186
ARP1	actin related protein 1A	*ACTR1A*	605143	376
CapZ	capping actin protein of muscle Z-line subunit alpha 1	*CAPZA1*	601580	286
β-actin	actin beta	*ACTB*	102630	375
ARP11	actin related protein 3B	*ACTR3B*	-	418
p62	dynactin subunit 4	*DCTN4*	614758	467
p25	dynactin subunit 5	*DCTN5*	612962	182
P27	dynactin subunit 6	*DCTN6*	612963	190

Column 1, non-standard subunit designations; column 2, official gene nomenclature (HGNC); column 3, gene symbol; column 4, OMIM reference numbers; column 5, number of amino acids. *DCTN1-3* are dynactin shoulder subunits; *ACTR1A, CAPZA1*, and *ACTB* are *ARP1* filament subunits; ACTR3B and DCTN4-6 are pointed end subunits.

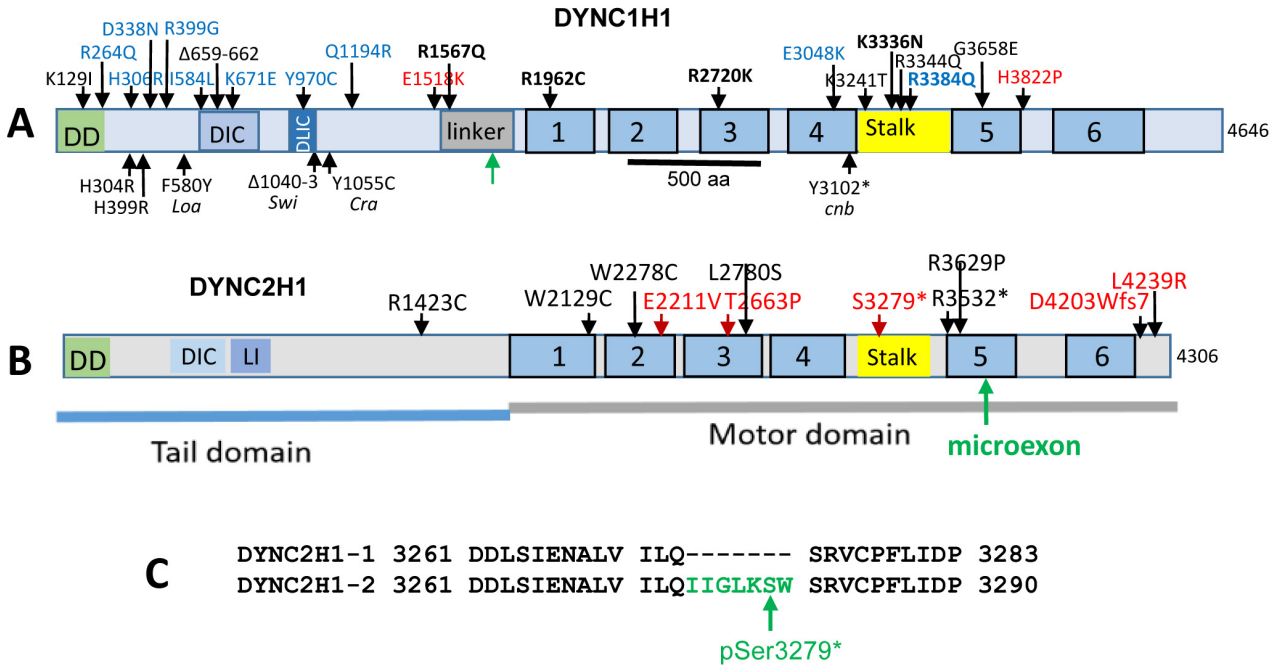

Figure 3. Disease-causing mutations of dynein heavy chain domains. **A**: DYNC1H1. DD, dimerization domain; DIC and DLIC are regions of interaction; the stalk specifies the area of microtubule binding. ATPase domains 1–6 (blue bars 1–6) are shown. Top, human mutations. Mutations causing intellectual disability (red); MCD (black); SMA-LED (blue). Bottom, mouse and zebrafish mutations. Green arrow, point of DYNC1H1 truncation in the linker region produced in the Six3Cre conditional knockout (^{ret}*Dync1h1*$^{-/-}$). **B**: DYNC2H1. Mutations associated with short-rib polydactyly syndrome (black) and nonsyndromic retinitis pigmentosa (RP; red) are indicated. **C**: Partial sequences of human Dync2h1 exons 63 and 65 flanking exon 64 (green) present only in isoform 2. A stop codon pS3279* is associated with nonsyndromic recessive RP.

neuronal migration [63]. *Loa* and *Cra1* mutations exhibit remarkable similarity to specific features of human pathology for amyotrophic lateral sclerosis (ALS) [64]. Homozygous *Loa* mice were unable to feed and died perinatally [60,63]. The *Swl* mouse carries a deletion of four amino acids (1040–1043) which are replaced by a single alanine [65]. *Swl*/+ mice also develop gait anomalies. A homozygous *Dync1h1*(H306R) mouse model survives postnatally with significant defects in motor skill and neuromuscular junction architecture, features reminiscent of CMT2O [66]. Potential *Loa, Cra1, Swl*, and *Dync1h1*(H306R) retina phenotypes have not been assessed.

Dynein heavy chain mutations affecting the zebrafish retina: A *dync1h1* nonsense mutation (Y3102X; Figure 3A) underlies the zebrafish *cannonball* (*cnb*) phenotype [18]. The truncated protein lacks the carboxyterminal one-third of Dync1h1, including the stalk domain where microtubule binding occurs, as well as the fifth and sixth ATPase motor domains, yet *cnb* embryos survive until the larval stage, presumably owing to maternal dynein mRNA stores [18]. Retinal photoreceptors, however, exhibit defects in organelle positioning, post-Golgi vesicle trafficking, and outer segment morphogenesis. Green fluorescent protein (GFP)-tagged rhodopsin mislocalized in the *cannonball* mutant and *dync1h1* morphant rods [18].

A mutation in the zebrafish *mikre oko* (*mok*) locus, which encodes the dynactin-1 subunit (p150^{glued} or DCTN1) of the dynein complex, results in severe basal displacement of nuclei toward synaptic terminals. Despite abnormal nuclear positioning, cell polarity, outer segment formation, and rhodopsin trafficking are normal in *mok* zebrafish during early development. *Mok* photoreceptors rapidly degenerate by 5 days postfertilization [67]. Basal body docking was unaffected in *cnb* and *mok* zebrafish [68].

Knockdown of *DYNC2H1* in zebrafish with morpholino oligonucleotides against heavy chain dync2h1, light intermediate chain dync2li1, and intermediate chain dync2i1 of cytoplasmic dynein-2 revealed an essential role for the dynein-2 complex for maintenance of the outer segments. Morphant photoreceptor connecting cilia were swollen, but neither opsin nor arrestin was mislocalized, although IFT88 accumulated in the connecting cilium distal region [69].

NINL and its novel interaction partner, DZANK1, play essential roles in vesicle transport toward the zebrafish photoreceptor outer segments [70]. NINL protein and double zinc ribbon and ankyrin repeat domains 1 protein (DZANK1) were shown to associate with DYNC1H1 and multiple dynein intermediate and light chains as well as actin-binding proteins. Knockdown of either *NINL* or *DZANK1* in zebrafish larvae leads to abnormal outer segment morphology, mislocalized rhodopsin, vesicle accumulation, and loss of visual function. The exact roles of NINL and DZANK1 in dynein-mediated transport are unclear.

Conditional Dync1h1 knockout in the mouse: Germline deletions of mouse *Dync1h1* (truncation after exon 1) are lethal, as embryos do not survive beyond E8.5 [71]. We recently generated a retina-specific deletion of *DYNC1H1* (^{ret}*Dync1h1*$^{-/-}$) in which exons 24 and 25 are excised from retinal progenitors using the Cre-loxP system [72]. Heavy chain truncation results in loss of the motor and microtubule-binding domain (Figure 3A; the green arrow identifies the truncation point). ^{ret}*Dync1h1*$^{-/-}$ photoreceptors degenerated rapidly within the first 2 postnatal weeks. Although the *Dync1h1* gene was effectively silenced by postnatal day 6 (P6), the DYNC1H1 protein persisted and aggregated together with rhodopsin, PDE6, and centrin-2-positive centrosomes in the outer nuclear layer. By P8, however, the outer and inner nuclear layers of ^{ret}*Dync1h1*$^{-/-}$ central retina were severely disorganized and lacked a recognizable outer plexiform layer (OPL; Figure 4B, right panel).

Active nuclear positioning in the mouse retina takes place in the first 2 postnatal weeks and is managed by two motors, dynein and kinesin-1, walking toward the minus and plus ends of microtubules, respectively [73,74]. In the P4 wild-type (WT) retina, the uniform neuroblastic layer does not show a continuous OPL with synaptic connections [75,76], but the OPL is well established by P6 (Figure 4A). However by P8, the outer and inner nuclear layers of the ^{ret}*Dync1h1*$^{-/-}$ central retina are severely disorganized and lack a recognizable OPL (Figure 4B, right panel). Additionally, the nuclear layer is often interrupted suggesting that the nuclei are not positioned correctly, a phenotype consistent with polarity defects [68,77-79]. Similar disorganization is observed when Syne2/Nesprin2 and Sun2, members of the LINC complex mediating nuclear migration during retina development, are deleted [80,81]. The results show that cytoplasmic dynein is essential for nuclear lamination, nuclear positioning, vesicular transport of photoreceptor membrane proteins, and elaboration of inner and outer segments.

As dynein participates in moving organelles and Golgi complex-derived vesicles, translocation and docking of the ciliary vesicle to the mother centriole may also be dynein-dependent. Docking of the basal body occurs in several unsynchronized steps in early postnatal development [82,83] as the mother centriole acquires a Golgi-derived ciliary vesicle that mediates docking to the plasma membrane [84]. However, that dynein may be dispensable for basal body docking during postnatal photoreceptor development was suggested following results of DYNC1H1 knockdown in zebrafish [68]. We performed an ultrastructural examination

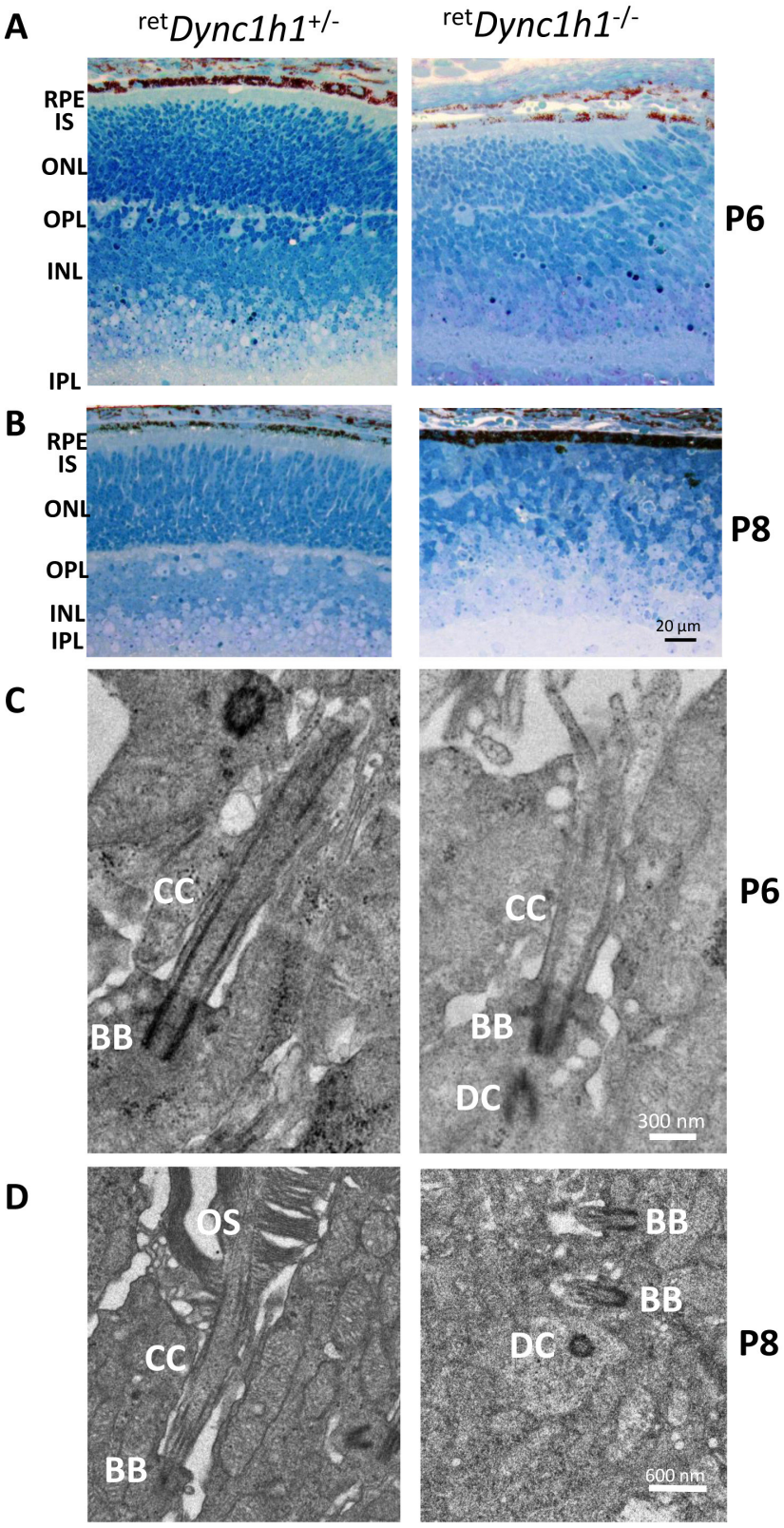

Figure 4. Defective $^{ret}Dync1h1^{-/-}$ retina lamination and impaired ciliogenesis. **A, B**: Plastic sections of the central retina near the optic nerve of heterozygous control (left) and $^{ret}Dync1h1^{-/-}$ (right) mice at P6 and P8. Sections are stained with methylene blue-Azure II (Richardson's) to demonstrate the retina layers. RPE, retinal pigmented epithelium; IS, inner segment; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer. Scale bar = 20 µm. **C**: Representative ultrastructure of connecting cilia emanating from heterozygous control (left panel) and $^{ret}Dync1h1^{-/-}$ basal bodies (right panel) at P6. Note the presence of the daughter centriole (DC), basal body (BB) docking to the membrane, and connecting cilium (CC) elaboration in the $^{ret}Dync1h1^{-/-}$ photoreceptor, scale bar = 0.3 µm. **D**: Axonemes and connecting cilia are absent at P8, scale bar = 0.6 µm. Left panel, heterozygous control; right panel, *Dync1h1* knockout mouse. Modified from [72] with permission from *PLOS One.*

that confirmed that the ^{ret}*Dync1h1*$^{-/-}$ basal body docks to the photoreceptor cortex at P6 and extends a connecting cilium (Figure 4C), thus corroborating that acquisition or docking of Golgi-derived ciliary vesicles is independent of dynein-1. The connecting cilium and the outer segments are lost by P8 (Figure 4D) indicating the necessity of dynein-1 for extension or maintenance of these structures.

Future directions: In photoreceptors, the identities of adaptors essential for cargo binding in vivo and how cargo (e.g., rhodopsin-bearing vesicles) may be bound to dynein-1/dynactin are unknown. Rhodopsin and other transmembrane proteins are synthesized by ribosomes attached to the endoplasmic reticulum (ER) membrane surrounding the nucleus, and correctly folded proteins exit in COPII-coated vesicles at specialized ER exit sites (reviewed in [85]). Cargo-containing vesicles then traffic, presumably bound to dynein/dynactin, through the Golgi to the trans-Golgi network (TGN). Following transition through Golgi stacks, cargo is sorted and packaged into TGN vesicles for delivery to their final destinations. In vitro motility assays of 20 years ago established that rhodopsin-bearing vesicles translocate along microtubules at a rate of about 1 µm/sec [86]. LC8 and TCTEX1 variants form a subcomplex with DICs, and they interact with numerous protein and ribonucleoprotein partners, leading to the hypothesis that these subunits serve to tether cargo to the dynein motor [86]. However, the structure of a complex of LC8 and TCTEX1 associated with their intermediate chain scaffold effectively blocks the major putative cargo binding sites [87], suggesting that LC8 and TCTEX do not bind cargo directly. Unraveling mechanistic details and identifying effectors for rhodopsin transport are worthwhile goals for future research.

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