HHS Public Access

Author manuscript

Curr Top Dev Biol. Author manuscript; available in PMC 2022 January 07.

Published in final edited form as:

Curr Top Dev Biol. 2021 ; 142: 99–146. doi:10.1016/bs.ctdb.2020.11.003.

The essential role of primary cilia in cerebral cortical development and disorders

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Abstract

Primary cilium, first described in the 19th century in different cell types and organisms by Alexander Ecker, Albert Kolliker, Aleksandr Kowalevsky, Paul Langerhans, and Karl Zimmermann (Ecker, 1844; Kolliker, 1854; Kowalevsky, 1867; Langerhans, 1876; Zimmermann, 1898), play an essential modulatory role in diverse aspects of nervous system development and function. The primary cilium, sometimes referred to as the cell's 'antennae', can receive wide ranging inputs from cellular milieu, including morphogens, growth factors, neuromodulators, and neurotransmitters. Its unique structural and functional organization bequeaths it the capacity to hyper-concentrate signaling machinery in a restricted cellular domain approximately one-thousandth the volume of cell soma. Thus enabling it to act as a signaling hub that integrates diverse developmental and homestatic information from cellular milieu to regulate the development and function of neural cells. Dysfunction of primary cilia contributes to the pathophysiology of several brain malformations, intellectual disabilities, epilepsy, and psychiatric disorders. This review focuses on the most essential contributions of primary cilia to cerebral cortical development and function, in the context of neurodevelopmental disorders and malformations. It highlights the recent progress made in identifying the mechanisms underlying primary cilia's role in cortical progenitors, neurons and glia, in health and disease. A future challenge will be to translate these insights and advances into effective clinical treatments for ciliopathies.

1. Introduction

Primary cilia are microtubule based antennae-like sensory organelles extended by a vast majority of mammalian cells (Bloodgood, 2009; Fliegauf, Benzing, & Omran, 2007; Hilgendorf, Johnson, & Jackson, 2016; Reiter & Leroux, 2017; Sengupta, 2017). Primary cilia are anchored to the cell by mother centriole, the older of the pair of centrioles, which together with the pericentrosomal matrix, make up the centrosome complex. The primary

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Declaration of competing financial interests

The authors declare no competing financial interests.

cilia are structurally and functionally distinct from the motile cilia, that line epithelia and power fluid movement (Ringers, Olstad, & Jurisch-Yaksi, 2020). Disruption of the physiological function of primary cilia in humans lead to a broad range of multi-organ disease phenotypes, including obesity, renal, hepatic, and pancreatic cyst formation, situs abnormalities, congenital heart defects, anosmia, retinal degeneration, postaxial polydactyly, bronchiectasis, hypogonadism, infertility, hearing loss, facial anomalies, liver fibrosis, and brain malformations (Fliegauf et al., 2007; Hildebrandt, Benzing, & Katsanis, 2011; Lancaster & Gleeson, 2009; McIntyre et al., 2012; Mitchison & Valente, 2017; Park, Jang, & Lee, 2019; Reiter & Leroux, 2017; Sattar & Gleeson, 2011; Thomas, Boutaud, Reilly, & Benmerah, 2019; Valente, Rosti, Gibbs, & Gleeson, 2014). These disorders resulting from aberrant primary cilia function include Bardet-Biedl syndrome (BBS), nephronophthisis (NPHP), Senior-Loken syndrome (SNLS), Alstrom syndrome (ALMS), Meckel syndrome (MKS), Joubert syndrome (JBTS), Oral-facial-digital Type I (OFD 1), polycystic kidney diseases (PKD), Jeune asphyxiating thoracic dystrophy (JATD), Ellis van Creveld (EVC), and Leber congenital amaurosis (LCA) (see Reiter & Leroux, 2017 and Ringers et al., 2020 for comprehensive reviews of motile and non-motile ciliopathies).

Abnormalities in the formation, connectivity, and function of the central nervous system (CNS) underlie the neurological syndromes triggered by primary cilia malfunction (Caspary, Larkins, & Anderson, 2007; Doherty, 2009; Guo et al., 2015; Novarino, Akizu, & Gleeson, 2011; Parisi, 2019; Romani, Micalizzi, & Valente, 2013; Valente et al., 2014). These neurological syndromes include developmental delay, intellectual disabilities, autism spectrum disorder, mood disorders, epilepsy, abnormal respiratory rhythms, hypotonia, ataxia, oculomotor apraxia, and mirror movement synkinesis. The structural anomalies such as microcephaly, neuronal heterotopia, disrupted neuronal layer malformation, absent or reduced growth and decussation of axonal tracts (e.g., superior cerebellar peduncles (SCP), corticospinal tract (CST), corpus callosum (CC), and central pontine tracts), and cerebellar hypoplasia associated with these functional outcomes indicate the significance of physiological function of primary cilia in progenitors, neurons, and glia during human CNS development (Doherty, 2009; Guo et al., 2015; Juric-Sekhar, Adkins, Doherty, & Hevner, 2012; Parisi, 2019; Romani et al., 2013; Valente et al., 2014).

The human cerebral cortex forms as a result of coordinated unfolding of a series of inter-related developmental events (Kwan, Sestan, & Anton, 2012; Molnár et al., 2019; Fig. 1A). During early embryonic development, an undifferentiated sheet of pseudostratified neuroepithelial cells in telencephalic vesicles end their interkinetic nuclear migration, spanning the apical–basal axis, and transform into radial glial progenitors. Radial glial cells (RGCs), through their function as a source of neurogenic progenitors and neuronal migratory guides, provide a template for the formation of the cerebral cortex. RGCs in the pallium divide symmetrically and asymmetrically to expand the pool of progenitors and generate neurons, respectively. During the neurogenic period, asymmetric division of RGCs generates cortical neurons and neurogenic intermediate progenitors (IPs) or outer radial glial cells (oRGCs). Symmetric proliferation of IPs and oRGCs serve to rapidly expand the cortical neuronal population, particularly the upper layer neurons. The cell soma of radial progenitors remain apically positioned in the ventricular zone, with a long basal process extending toward the pial surface, thereby enabling the orderly generation and

guidance of new neurons in the cerebral cortex. Migration of clonally related neurons along related radial glial basal processes leads to the formation of cortical radial columns (or radial units) and laminar organization of neurons. As neurogenesis nears its completion, progenitors either morphologically transform or undergo a final division to generate astrocytes. Oligodendrocytes are generated similarly from progenitors in the subpallium. In contrast, microglia, originating from early erythromyeloid progenitors (EMPs) in the extra-embryonic yolk sac, enter the CNS in association with waves of hematopoiesis, prior to the proliferation of neural progenitors (Thion, Ginhoux, & Garel, 2018). The developmental balance between different progenitor subtypes and the resultant differences in the generation and guidance of distinct classes of neurons and glia within the developing cerebral cortex enables the emergence of distinctly different cortical areas with characteristic patterns of neuronal and glial density and diversity. Once appropriately positioned, connectivity between the two main types of neurons, excitatory projection neurons with spiny dendrites and long axons and inhibitory interneurons with short axons and non-spiny dendrites, form the basic neuronal circuitry in the cerebral cortex. The distinct cellular architecture of these neuronal subtypes and their interactions with glia (i.e., astrocytes, oligodendroglia, and microglia) constrains the types of circuits formed and thus the excitatory/inhibitory (E/I) balance and the functional competence of these cortical circuits. Primary cilia play a diverse and essential modulatory role in these major developmental events underlying cerebral cortical formation and function (Fig. 1B-M).

The majority of the cellular components of the developing cerebral cortex, including neuroepithelial cells, progenitors, migrating neurons, postmigratory neurons, and astrocytes, have active primary cilia (Fig. 2; Arellano, Guadiana, Breunig, Rakic, & Sarkisian, 2017; Bishop, Berbari, Lewis, & Mykytyn, 2007; Green & Mykytyn, 2014; Guemez-Gamboa, Coufal, & Gleeson, 2014; Sarkisian & Guadiana, 2015; Sengupta, 2017). Presence of primary cilia in mature oligodendrocytes and microglial cells has yet to be conclusively demonstrated. Primary cilia in the developing cortical cells are highly dynamic in terms of their ability to undergo changes in shape, length, and orientation during development (Fig. 2B; Higginbotham et al., 2012, 2013). Although the detection of primary cilia in different cortical cells with transmission or scanning electron microscopy analyses or immunolabeling with pancilia-specific antibodies (e.g., anti-ACIII or Arl13b) do not reveal their functional diversity, primary cilia in each of these cell types are highly likely to be specialized to subserve cell-type specific functions during cortical development. Supporting this possibility, expression mapping of cilia-associated genes across different cell types during cerebral cortical development reveals distinct cell-type specific expression profiles (Loo et al., 2019; Fig. 3). How this molecular specification of primary cilia in different cortical cells translates into developmental stage- and cell type-specific functions during cerebral cortical formation remains open. However, the spectrum of primary cilia related developmental brain malformations indicate the significance of this sensory organelle for the appropriate development and differentiation of cortical progenitors, neurons, and glia and the resultant orderly progression of cerebral cortical formation and organization.

2. Progenitors, primary cilia, and associated brain developmental malformations

The organization of the ventricular niche where radial glial cells, intermediate progenitors, and outer radial glial progenitors actively form, divide, and interact with their daughter neuron or glial cells, depends on primary cilia signaling (Guo et al., 2015; Higginbotham et al., 2013; Lepanto, Badano, & Zolessi, 2016; Valente et al., 2014). In proliferating progenitors, primary cilia are disassembled during cell division and ciliary membrane remnants may preferentially associate with the mother centriole. During neurogenesis, asymmetric inheritance of the old mother centriole by daughter radial glial progenitors facilitates the maintenance of radial progenitor identity (Wang et al., 2009). Asymmetric inheritance of the primed mother centriole and thus, rapid extension of a primary cilium by one of the daughter cells is thought to provide differential competence for that daughter cell to respond to environmental cues in the ventricular niche (Basten & Giles, 2013; Delgehyr & Spassky, 2014). In dividing radial progenitors, WDR62 enables centrosome protein CEP170's localization to the basal body of the primary cilium, where CEP170 recruits a microtubule depolymerizing factor, KIF2A, to dismantle the cilium (Zhang et al., 2019). Disruption of this pathway and other WDR62 linked networks vital for cilia formation (e.g., WDR62-CPAP-IFT88) lead to microcephaly (Shohayeb et al., 2020; Zhang et al., 2019).

Disruption of primary cilia activity in early radial progenitors via Arl13b deletion disrupt their apical-basal polarity, leading to drastic malformation of the cerebral cortex (Higginbotham et al., 2013). Shh mutations in humans, likely disrupting cilia mediated Shh signaling, lead to holoprosencephaly where defective early patterning of neuroepithelial cells results in the failure of the forebrain to develop into two cerebral cortical hemispheres (Fig. 1B and C; Monuki & Walsh, 2001; Nanni et al., 1999). Further, primary cilia in RGCs regulate the size of the surface of their ventricular apical domains via the mTORC1 pathway. Genetic deletion of primary cilia in RGCs (via conditional deletion of *Ift88* or *Kif3a* in RGCs) leads to misorientation of the mitotic spindle in radial glia, increased basal progenitors, dilation of brain ventricles (ventriculomegaly), and eventual hydrocephalus (Foerster et al., 2017). In contrast to RGCs, the dynamics and significance of primary cilia in intermediate progenitors and outer radial glia remains to be fully defined. In the postnatal germinal niche of the forebrain, the ventricular–subventricular zone, where there is ongoing progenitor proliferation and neurogenesis, the primary cilia is required for neurogenesis (Tong et al., 2014).

Several human ciliopathy mutations that disrupt ciliogenesis in progenitors, primarily via disrupting centrosome or centriolar functions, lead to primary microcephaly (Fig. 1D), where disrupted progenitor proliferation causes a reduction in the generation of appropriate complement of neurons and glia necessary to form a normal cerebral cortex. For example, mutations in centrosome related genes PCNT, PLK4, ASPM, WDR62, CPAP, DNYLT1, and C2CD3 disrupt appropriate patterns of ciliogenesis or cilia maintenance, post cell-division, thus disrupting the ability of progenitors to use primary cilia to sense essential environmental cues present in the CSF (e.g., SHH) or ventricular niche (e.g., IGF) necessary

for progenitor differentiation (Bilguvar et al., 2010; Bober & Jackson, 2017; Boczek et al., 2018; Bond et al., 2002; Gabriel et al., 2016; Lehtinen et al., 2011; Li et al., 2011; Nicholas et al., 2010; Thauvin-Robinet et al., 2014). In addition, mutations in genes necessary for primary cilia structural maintenance, trafficking, or signaling, such as KIF2A, RPGRIP1L, Arl13b or Inpp5e, also disrupt the ventricular niche of the developing cerebral cortex and leads to microcephaly or subcortical heterotopia (Bielas et al., 2009; Broix et al., 2018; Cavallin et al., 2017; Higginbotham et al., 2013; Poirier et al., 2013; Uzquiano et al., 2019). Microcephaly in humans is often presented with hydrocephalus. Many of the genes disrupting primary cilia in progenitors can also affect motile cilia in ependymal cells lining the ventricles necessary for CSF flow. This may contribute to defective ependymal cell differentiation, ciliogenesis, and or motile ciliary beating frequency changes in these cells and thus hydrocephaly (Ringers et al., 2020).

Opposite of microcephaly, megalencephaly results from over proliferation of progenitors. Removal of CEP83 in RGCs disrupts distal appendage (DAP) assembly and thus impairs the anchoring of the centrosome to the apical membrane and primary ciliogenesis (Shao et al., 2020). CEP83 deficiency leads to megalencephaly and biallelic mutations in human *CEP83* cause intellectual disability (Failler et al., 2014). Furthermore, an activating mutation of AKT in humans cause hemimegalencephaly (Poduri et al., 2012). Primary cilia activation leads to phospho AKT localization at the base of primary cilium (Christensen, Morthorst, Mogensen, & Pedersen, 2017; Suizu et al., 2016). If and how the primary cilium is affected in human cortical progenitors with AKT mutations and how it contributes to brain overgrowth in these patients remains to be fully examined.

3. Migrating neurons and primary cilium in the developing cerebral cortex

Following their birth in the ventricular zone, newborn neurons migrate several thousand cell soma size distances through a complex cellular milieu to reach their final resting position in different cortical layers and areas. Both radially migrating projection neurons and tangentially migrating interneurons in the cerebral cortex display a dynamic primary cilium. Primary cilia change in length, rotate, branch, and appear to probe their surroundings in migrating inter neurons (Higginbotham et al., 2012). Cilia in neurons localize to the leading process during migration, but move closer to the cell soma during periods of pausing when they became much more dynamic in their movement and length. Electron tomography studies of interneuronal primary cilia further indicate that they cycle between elongated, surface-exposed and shorter, intracellular phases, in coordination with the cell migration stages (Baudoin et al., 2012). The localization and orientation of the primary cilium are also altered depending on the state of migration in migrating neuroblasts of the postnatal rostral migratory stream (Matsumoto et al., 2019). In contrast, signaling defective primary cilia in neurons do not display such dynamism (Higginbotham et al., 2012). Neurons with mutant cilia paused longer during migration and were unable to respond to micro gradients of guidance cues, suggesting that the reduction in cilia dynamics may reflect an inability to efficiently sense guidance cues in the migratory environment (Higginbotham et al., 2012).

Intriguingly, primary cilia activity modulates both radially and tangentially migrating neurons in the cerebral cortex (Baudoin et al., 2012; Guo et al., 2015; Higginbotham et al.,

2012; Park et al., 2018). Radial migration involves close intercellular adhesive interactions with radial glial migratory guides, whereas tangential migration occurs for the most part in a cell-substrate independent manner. After they invade the developing cerebral wall, tangentially migrating neurons turn radially, along radial glia processes, to populate the emerging cortical layers (Yokota et al., 2007). Neuronal primary cilia are hypothesized to cell autonomously bind and transduce signals from gradients of guidance molecules, leading to changes in neuronal morphology and movement (Higginbotham et al., 2012). Shh signaling via primary cilia may enable tangentially migrating interneurons to turn radially and populate appropriate cortical plate regions (Baudoin et al., 2012). However, primary cilia may differentially affect the chemotaxic and haptotaxic mechanisms necessary for radial or tangential neuronal migration. Further, it remains untested if primary cilia and the growth cones in the leading processes of migrating neurons transduce different signals related to the directed movement of neurons.

Human genetic mutations of EML1 that perturb anterograde trafficking from the Golgi apparatus to primary cilia and thus the maintenance of primary cilia, lead to subcortical heterotopia, characterized by ectopic radial progenitor localization, disrupted neuronal migration, and aberrant placement of neurons away from their predestined cortical layers (Fig. 2F and G; Uzquiano et al., 2019). *RTTN* mutations associated with dysmorphic primary cilium can cause lissencephaly (Fig. 2E), a cortical neuronal migration defect resulting from an inability to properly maintain neuronal migration during cortical development (Kwan et al., 2012; Shamseldin et al., 2015). *MTOR* mutations affecting autophagy mediated ciliogenesis disrupts radial neuronal migration and leads to focal cortical dysplasia in FMCD patients with somatic mutations in *MTOR* (Di Nardo & Sahin, 2018; Park et al., 2019, 2018). MTOR mutant neurons without primary cilium or severely shortened primary cilium do not undergo normal radial migration and appropriate laminar placement when compared to wild type neurons in the same brain (Park et al., 2018), further demonstrating a role for primary cilia signaling in cortical neuronal migration.

Recent studies combining real time neuronal migration assays with live imaging of second messenger pathways in the ciliary compartment are beginning to provide new insights into how directional information from guidance cues in the developing cortex may be conveyed through the primary cilium to trigger changes in neuronal migration (Stoufflet et al., 2019). In embryonic, postnatal and adult migrating neurons, ciliary Adenylate Cyclase 3 (AC3) activity generates cAMP, which in turn activates centrosomal Protein Kinase A (PKA). Live-imaging with cAMP biosensors reveals a periodic cAMP hotspot at the centrosome, which appears to be necessary for centrosome/nucleus coupling and nucleokinesis of neurons. Delocalization of PKA from the centrosome leads to migratory defects. Primary cilia and its anchoring centrosome may form a cAMP-signaling unit to dynamically regulate neuronal migration (Stoufflet et al., 2019). Considering the cilium's proximity to the nucleus and its link to the centrosome-associated microtubule network, such primary cilia generated cAMP-signaling may promote rapid and efficient local and transcriptional signal transduction underlying nucleokinesis and directional migration of neurons.

4. Dendrites, axons, neuronal connectivity and primary cilium

As neurons arrive at their appropriate laminar locations, they extend dendrites and axons to form appropriate connections with other neurons in cortex and sub cerebral regions (Banker, 2018; Barnes & Polleux, 2009). Axonal pathway defects are a common feature in many human ciliopathies (Guo et al., 2015; Reiter & Leroux, 2017; Valente et al., 2014; Fig. 2J-M). Appropriate axonal growth and pathfinding are essential for the wiring of the developing brain (Chedotal & Richards, 2010; Engle, 2010). Joubert Syndrome Related disorders (JSRD), a subset of ciliopathies, are characterized by consistent and distinct axonal malformations (Brancati, Dallapiccola, & Valente, 2010; Engle, 2010; Parisi, 2009). An axonal tract malformation called the molar tooth sign (MTS) is a diagnostic feature of JSRD. MTS results from thickened, elongated, and horizontally misoriented superior cerebellar peduncles (SCPs) that fail to decussate in the midbrain (Brancati et al., 2010; Juric-Sekhar et al., 2012; Parisi, 2009; Sattar & Gleeson, 2011; Senocak, Oguz, Haliloglu, Topcu, & Cila, 2010). SCPs are formed by the axons of deep cerebellar nuclei (DCN). In addition to SCP malformation, absent or reduced decussation of the corticospinal tract (CST), corpus callosum (CC), and transverse pontine tracts are frequently observed in JSRD patients (Brancati et al., 2010; Engle, 2010; Hildebrandt et al., 2011; Jissendi-Tchofo et al., 2015; Juric-Sekhar et al., 2012; Poretti et al., 2007; Romani et al., 2013). Consistent with these axonal anomalies and the resultant changes in brain wiring, JSRD patients are often diagnosed with delayed development, intellectual disabilities, autism spectrum disorder (ASD), muscular hypotonia, breathing difficulties, epilepsy, and ataxia (Akizu et al., 2013, 2014; Alvarez Retuerto et al., 2008; Novarino et al., 2011; Reiter & Leroux, 2017). Further, mutations in KIF7, a ciliary kinesin, leads to callosal agenesis or hypoplasia with associated intellectual disabilities (Putoux et al., 2011; Fig. 2J-K). Callosal axon malformations are also seen in ciliopathies such as Oral-facial-digital Syndrome resulting from mutations in OFD1 or TCTN3, necessary for centriole elongation and ciliogenesis or transition zone organization and SHH signaling, respectively (Guo et al., 2015; Thauvin-Robinet et al., 2013; Thomas et al., 2012). These diverse axonal phenotypes related to primary cilia malfunctions in humans strongly indicate the significance of ciliary signaling to axonal tract growth and connectivity.

During the formation of neuronal connectivity in the brain, axons are guided by tropic and trophic gradients of chemoattractant or chemorepellent cues toward their target. Axons extend in large tracts or fascicles and follow stereotyped pathways to reach their appropriate synaptic targets in distant brain regions. Such group extension of axons toward appropriate targets is necessary for neuronal wiring in the brain (Barnes & Polleux, 2009; Chedotal & Richards, 2010; Cionni et al., 2018; Engle, 2010; Paolino, Fenlon, Suárez, & Richards, 2018). The axon-dendrite polarization of neurites and initial extension of axons appear to be unaffected in the absence of primary cilia signaling (Guo et al., 2019). However, branching, fasciculation and crossing of axons and thus their accurate final projections and connectivity are disrupted in cilia mutants (Grochowsky & Gunay-Aygun, 2019; Guo et al., 2015; Parisi, 2019; Poretti, Huisman, Scheer, & Boltshauser, 2011; Qian, Song, & Ming, 2019; Thomas et al., 2019; Ware, Gunay-Aygun, & Hildebrandt, 2011). How does primary cilia signaling selectively modulate the fasciculation, decussation, and targeting of axons?

A motile growth cone that properly responds to guidance cues, and axon-axon interactions that enable axon sorting and fasciculation are both crucial to ensure the fidelity of axonal growth and navigation during development (Nishikimi, Oishi, & Nakajima, 2013; Raper & Mason, 2010; Wang & Marquardt, 2013; Yu & Bargmann, 2001). The axonal growth cone motility and direction relies on the interplay between filopodia that sense environmental cues for pathfinding, and lamellipodia that support persistent axonal outgrowth (Mattila & Lappalainen, 2008; Mejillano et al., 2004). Growth cones of neurons with aberrant primary cilia show altered filopodia vs. lamellipodia balance (Guo et al., 2019). Further, adhesion molecules such as Pcdh17, essential to mediate axon-axon recognition (Hayashi et al., 2014; Hoshina et al., 2013), fail to localize to axon-axon contacts along cilia mutant axonal shafts (Guo et al., 2019). The combined disruption in axonal growth cone dynamics and axon-axon interactions may thus contribute to the axonal pathfinding and fasciculation defects evident in neurons with defective primary cilia (Guo et al., 2015, 2019). Some of the axonal tract defects in ciliopathies, particularly callosal malformations, may also involve abnormal guidepost cell positioning and associated inappropriate midline crossing (Laclef et al., 2015; Putoux et al., 2019).

Once they reach their appropriate targets, axons establish proper connections by extending terminal axon arbors (Courchet et al., 2013; Gibson & Ma, 2011; Kalil & Dent, 2014; Kalil, Li, & Hutchins, 2011). Upper layer cortical neurons with disrupted cilia grow a long primary axon with significantly reduced terminal arbors at targets in ipsi and contra lateral cortex, thus failing to sufficiently innervate their targets to form appropriate neuronal connections (Guo et al., 2019). Neuron intrinsic properties (e.g. neuronal activity, cAMP and Ca^{2+} gradients) are known to converge onto signaling nodes (e.g. PI3K/AKT/GSK3β, Rho GTPases) to shape axonal growth, branching and targeting (Kalil & Dent, 2014). But how do primary cilia convey such signals to axons?

The primary cilium, with a volume ~1/1000 of the soma (Phua, Lin, & Inoue, 2015), is home to diverse signaling machineries, including receptor tyrosine kinases (e.g., IGFR, EGFR, MET, PDGFR-α, Trk receptors $p75^{NTR}$ and TrkB; (Armato, Chakravarthy, Chiarini, PrÃ, & Whitfield, 2011; Christensen, Clement, Satir, & Pedersen, 2012) and GPCRs (e.g., Smo, Frizzled receptor FZD3, Sstr3, HTR6, NPY2R, NPY5R, DRD1, DRD2, MchR1, GPR161, GPR120 (Choi et al., 2011; Christensen et al., 2012; Green & Mykytyn, 2014; Hilgendorf et al., 2016; Mukhopadhyay & Rohatgi, 2014; Nichols, Floyd, Bruinsma, Narzinski, & Baranski, 2013; Omori et al., 2015; Schou, Pedersen, & Christensen, 2015), their downstream effectors (e.g., PI3 kinase (Franco et al., 2014), Inpp5b, Inpp5e (Conduit, Dyson, & Mitchell, 2012; Jacoby et al., 2009), Ocrl (Phua et al., 2015), AKT (Zhu, Shi, Wang, & Liao, 2009), AC3, 5 and 6 (Phua et al., 2015), and second messengers (e.g., PIP3, PIP2, Ca^{2+} and cAMP; (DeCaen, Delling, Vien, & Clapham, 2015; Delling, DeCaen, Doerner, Febvay, & Clapham, 2013). The primary cilium thus provides a unique environment where signaling components are highly concentrated in a small cellular domain to rapidly trigger and facilitate efficient signaling cascade activation and crosstalk (Gherman, Davis, & Katsanis, 2006; Ishikawa, Thompson, Yates, & Marshall, 2012; Kohli et al., 2017; Narita, Kozuka-Hata, Nonami, et al., 2012; Sigg et al., 2017; Van Dam et al., 2019, 2013; Mick et al., 2015).

Using optogenetic or chemogenetic methods to exert precise control of cilia-specific signaling events, the cellular and physiological impact of the signaling emanating selectively from the primary cilium on developing neurons and neural circuit formation are beginning to be understood (Guo et al., 2017, 2019). Optogenetic or chemogenetic manipulation of ciliary signaling events at multiple levels, including receptor activation (e.g., GPCRs), downstream effector activation (e.g., PI3K, AKT), and second messenger production (i.e., cAMP via ACIII), reveal that exogenously induced deregulation of ciliary signaling cascades rapidly alters growth cone behavior and filopodia/lamellipodia balance, to a large extent recapitulating the aberrant axonal growth cone behavior seen in primary cilia mutant neurons. Conversely, activation of the ciliary-phosphoinositide phosphatase (Inpp5e) pathway, that antagonizes PI3K/AKT signaling, induces an opposite effect, causing axons to retract filopodia and extend lamellipodia. These results suggest that disrupted primary cilia driven PI3K/AKT signaling homeostasis may be an underlying cause of aberrant axonal growth dynamics in cilia mutant neurons and that signals emanating from primary cilia have the capacity to remotely and rapidly regulate axonal growth behavior (Guo et al., 2015, 2019).

Once triggered, PI3K/AKT signaling co-opts downstream kinase cascades and second messengers (e.g. Ca^{2+}, cAMP, IP3, PIP3) to amplify and propagate signals for cell-wide, long-distance signaling (Civelli, 2012; Gavi, Shumay, Wang, & Malbon, 2006; Lemmon & Schlessinger, 2010). Ciliary GPCR signaling can induce axonal Ca^{2+} waves down to the growth cone (Guo et al., 2019). Localized activation of GPCR or PI3K/AKT signaling are known to trigger cell-wide Ca^{2+} waves through Ca^{2+} influx via Ca^{2+} channels on the plasma membrane, IP3-mediated Ca^{2+} release from ER internal stores, and Ca^{2+}/calmodulin signaling mediated by calcium binding proteins such as CaMKII (Averaimo & Nicol, 2014; Henle et al., 2011; Schneider et al., 2008; Zheng & Poo, 2007). Various Ca^{2+} channels localize to primary cilia (e.g., PKD1-L1 and 2-L1; DeCaen et al., 2015; Phua et al., 2015; Pablo, DeCaen, & Clapham, 2017). CaMKIIβ, known to amplify Ca^{2+} signals, is localized to the base of cilia (Puram et al., 2011). Furthermore, Shh-Smo signaling, likely mediated via primary cilia, can downregulate cAMP levels and protein kinase A activity in commissural neurons to allow Sema3-mediated repulsion of commissural axons at midline crossing (Parra & Zou, 2010). Even though the exact mechanisms that enable ciliary signaling to trigger axonal Ca^{2+} wave and its integration with axonal PI3K/AKT signaling waves are yet to be fully elucidated, signaling effectors downstream of PI3K/AKT, such as TSC/mTOR, GSK3β, and CREB, are known to regulate cytoskeleton organization, transcriptional and translational programs involved in neuronal morphogenesis and synaptic plasticity. Particularly, human patients and genetic models with mutations in PI3K/AKT signaling pathway components (e.g. PTEN, AKT1, TSC1/2) show aberrant axonal growth and disorganization of axon tracts (Choi et al., 2008; Geoffroy et al., 2015; Huang, Chen, & Page, 2016; Kwon et al., 2006; Shin et al., 2017; Tsai & Sahin, 2011). Elevated PI3K/AKT activity and altered downstream mTOR, GSK3β and CREB activity were evident in JSRD-related mouse neuronal cilia mutant models (Guo et al., 2017, 2019; Higginbotham et al., 2012). Further, transcriptional networks modulated by JSRD genes such as ARL13B and ZNF423 converge onto neuronal developmental programs including neuronal differentiation, cytoskeleton organization, and neural survival, potentially through AKT signaling network

(Guo et al., 2019). These observations raise the intriguing hypothesis that PI3K/AKT signaling may serve as a converging node to integrate ciliary receptor signaling necessary for both rapid axonal growth modulation and long-term neuronal development programs.

Primary cilia signaling is known to modulate dendritic branching and spine formation in cortical neurons, possibly via cAMP and Shh-dependent pathways (Guadiana et al., 2013; Guo et al., 2017; Harwell et al., 2012; Lesiak, Brodsky, Cohenca, Croicu, & Neumaier, 2018). Disrupting primary cilia signaling via overexpression of 5HT6 and SSTR3 in cortical neurons, induces the formation of elongated and branched primary cilia, increases levels of intraflagellar transport proteins such as Kif3a, and reduces dendritic outgrowth and branching. These deficits are rescued when ciliary signaling capacity is restored with ACIII (Guadiana et al., 2013).

Intriguingly, both dendritic spines and cilia share a common function, i.e., to sense and transduce extracellular signals, with cilia being receptive to a broader range of extracellular cues than dendritic spines, which receive input signals primarily from presynaptic neurons and surrounding astrocytes or microglia (Nechipurenko, Doroquez, & Sengupta, 2013: Thion et al., 2018). Despite this commonality, if and how they influence each other remains an open question in neuronal functional biology. Intriguingly, synaptic integration that occurs in dendritic spines appears to require a functional primary cilium. Conditional deletion of cilia in hippocampal neurons induced defective dendritic refinement and synapse formation (Kumamoto et al., 2012). Importantly, unlike major axonal pathway defects detectable in MRI of ciliopathy patient brains, neuronal dendritic disruptions are yet to be systematically probed in genotyped ciliopathy patient brain tissue or organoid models.

5. Primary cilia's impact on neural circuit maintenance and function

In ciliopathies such JSRD, nearly two thirds of the affected individuals function in the intellectually disabled range, indicative of ongoing neural circuit malfunction (Grochowsky & Gunay-Aygun, 2019; Parisi, 2019). Psychomotor delay and epilepsy in subsets of ciliopathy patients further indicates neural circuit disruptions (Canning et al., 2018; Grochowsky & Gunay-Aygun, 2019). DISC1, a major susceptibility gene for psychiatric syndromes, regulates the formation and maintenance of primary cilia and targeting of dopamine D2 receptors to ciliary membrane (Marley & von Castro, 2012; Marley & von Zastrow, 2010). A diverse number of neuro-psychiatric risk genes affect the formation or maintenance of primary cilia (Marley & von Castro, 2012). A decrease in the percentage of cells (olfactory neuronal precursors [ONP]) with primary cilia was noticed in schizophrenia (SCZ) and bipolar disorder (BD) patients (Muñoz-Estrada, Lora-Castellanos, Meza, Alarcón Elizaldes, & Benítez-King, 2017). Missense mutations in RTTN or AH1, resulting in short and dysmorphic primary cilia, cause polymicrogyria, characterized by abnormal cortical neuronal organization and circuits (Fig. 1H and I; Dixon-Salazar et al., 2004; Kheradmand Kia et al., 2012). Lithium, a commonly used antimanic mood stabilizer, elongates primary cilia (Miyoshi, Kasahara, Miyazaki, & Asanuma, 2009; Muñoz-Estrada et al., 2017) and is known to rescue brain malformations in mouse models of JSRD ciliopathy (Ferland et al., 2004). Interneurons (INs) with Arl13b deficient primary cilia ($Arl13b^{cKO\text{-}IN}$) display reduced synaptic bouton density and size (Guo et al., 2017).

Patch-clamp electrophysiological recordings of interneuron-projection neuron circuits in brains with defective interneuronal primary cilia indicate a decrease in mIPSC frequency in projection neurons (Guo et al., 2017). In contrast, no changes in mIPSC amplitude, mEPSC frequency, or mEPSC amplitude were evident. The specific decrease in the inhibitory synaptic input onto projection neurons in cilia mutant mice ($Arl13b^{cKO\text{-}IN}$), leads to excitatory/inhibitory (E/I) synaptic imbalance in the IN-PN circuit. Intriguingly, accumulation and expression of somatostatin receptor 3 (Sstr3), a neurotransmitter receptor, is disrupted in the primary cilia of Arl13b deficient INs. Normal ciliary signaling involves ectocytosis of activated Sstr3 from ciliary tips (Nager et al., 2017). Disrupted ciliary targeting of neurotransmitter receptors such as Sstr3 may underlie cilia driven E/I imbalance in these mice. Consistent with this possibility, induced expression of Sstr3 in cilia mutant interneurons rescues their synaptic and E/I imbalance deficits (Guo et al., 2017). These observations indicate that primary cilia signaling is a non-synaptic signaling mechanism through which environmental signals can shape and refine interneuronal networks and this mechanism might be compromised in ciliopathy patients with neuro-behavioral or epilepsy phenotypes.

6. Glial diversity (astrocytes, oligodendrocytes, microglia), function, and primary cilia in the developing cerebral cortex

Primary cilia functions and signaling in developing glial cells (astrocytes, oligodendendrocytes, and microglia) of the central nervous system remain for the most part uncharacterized. The vast majority of astrocytes in the postnatal cerebral cortex express an individual primary cilium (Kasahara, Miyoshi, Murakami, Miyazaki, & Asanuma, 2014). Primary cilia signaling is necessary for the neurogenic function of astrocyte like precursors in mature hippocampus (Breunig et al., 2008; Han et al., 2009). Altered functional states such as seizure activity shortens astroglial cilia length (Sterpka et al., 2020). In contrast, primary cilia are either absent or severely malformed in aberrantly proliferating, invasive astrocytes in astrocytomas or gliomas (Basten & Giles, 2013; Han et al., 2009; Han & Alvarez-Buylla, 2010; Moser, Fritzler, & Rattner, 2009; Sarkisian & Semple-Rowland, 2019; Seeger-Nukpezah & Golemis, 2012). Primary cilia are present in oligodendrocyte precursor cells and ciliary Shh signaling is critical for the generation of myelinating oligodendrocytes from these precursors (Bhattarai, 2015; Falcon-Urrutia, Carrasco, Lois, Palma, & Roth, 2015; Sanchez & Armstrong, 2018). Although loss of primary cilia in differentiated oligodendrocytes was noticed in vitro (Falcon-Urrutia et al., 2015), the presence of primary cilia in subsets of myelinating mature oligodendrocytes in vivo remains possible (Sanchez & Armstrong, 2018). Immunolabeling with common primary ciliary markers such as ACIII did not detect primary cilia in microglial cells. However, the lack of primary cilia in these cells remains to be fully validated with the use of other established ciliary markers and electron microscopy analysis. Further, comprehensive characterization of the presence and function of primary cilia in different glial cells of the cerebral cortex, spanning the entire spectrum of cortical development, is necessary to fully evaluate the functional impact of glial primary cilia in cerebral cortex.

7. Future directions: Primary cilia's role in brain development and neurodevelopmental disorders

The primary cilium is structured and positioned to be able to generate a fast and robust response to a wide range of extracellular signals present in the cellular milieu of the developing brain. The diffusion barrier at the base of the cilium allows a cell to maximize the local concentration of a plethora of signaling receptors and their downstream effectors within cilia. The design of the primary cilium enables high levels of second messengers to be sustained more easily within the narrow geometry of the cilium than in other regions of the cell where diffusion through a larger space could lead to a rapid diminishment of the signal. The primary cilium's proximity to the nucleus and its link to the centrosome-associated microtubule network may promote rapid and efficient intracellular signal transduction. Understanding in real time how signaling emanating from primary cilia is conveyed to far flung domains of a neuron, including, dendritic, spines, axonal growth cones, AIS, and nucleus (or similarly, between primary cilium and distinct cell domains in non-neural cell types of the CNS) will be essential to fully evaluate the cell biological significance of this sensory organelle in nervous system development and disease (Fig. 4). Further, understanding the crosstalk that occurs between intracellular signaling cascades that originate in distinct cellular compartments (e.g., primary cilium, growth cone, dendritic spine, glial end feet etc.) of neural cells during development will help define the primary cilia-specific pathways vital for normal CNS development.

Considering that the vast majority of ciliopathies have their origins in primary cilia malfunction during embryonic development (Fig. 3), better modeling of cilia dysfunction and rescue in relevant human models, such as iPSC derived brain organoids, or exploration of CRISPR/Cas9-based targeted editing of ciliary gene defects *in utero* during development will help open up new therapeutic strategies to address ciliopathies at their origin.

Centrosomes play an essential role in ciliogenesis and cilia maintenance. Often human mutations affecting primarily the centrosomes lead to secondary structural and functional changes in primary cilia, causing a spectrum of outcomes not entirely attributable to primary cilia signaling. Further development of unbiased screening assays for the discovery and interrogation of mutations that exclusively affect the signaling function of neuronal or glial primary cilium and its underpinning cilia-specific machinery will shed new light on the functional importance of primary cilia in the nervous system.

Neuronal or glial primary cilia may produce a "ciliary signaling signature" that elicits cilia-specific impact on neuronal or glial events such as calcium waves, second messenger cascades, cytoskeletal rearrangements, adhesion, and transcriptional regulation necessary for proper neuronal or glial generation, growth, differentiation, and interactions. In this regard, examining if primary cilia in distinct cell types are as molecularly specified as the cell types they subserve, will be highly informative. Future efforts to decipher the precise molecular mediators of communication between neuronal or glial cilia and their cellular environment in the context of brain development will enable us to decisively delineate how primary cilia convey environmental signals to modulate brain formation and organization. Since ciliary proteins, such as Arl13b, can also exert cilia-independent functions in neural cells (Ferent et

al., 2019), a vigilant approach that excludes non-ciliary functions of cilia localized proteins should be part of this effort.

The neural circuit malfunctions associated with ciliopathies highlight the importance of investigating the possible participation of primary ciliary signaling in experience-driven refinement of cortical neuronal connectivity during critical periods or during learning and memory (Baraban et al., 2009; Chattopadhyaya et al., 2004; Southwell, Froemke, Alvarez-Buylla, Stryker, & Gandhi, 2010). Intriguingly, IGF1, a ligand for lgf1 R receptors in cilia (Higginbotham et al., 2013; Lehtinen et al., 2011), has been identified as a sensory experience regulated gene necessary to sculpt the synaptic connections of vasoactive intestinal peptide INs (Mardinly et al., 2016). In neurodegenerative disorders such as Huntington disease (HD), pathogenic polyQ expansion of huntingtin (HTT) protein causes centrosomal accumulation of PCM1 and abnormally long primary cilia in striatal cells, contributing to dysregulated circuit homeostasis in this disease (Keryer et al., 2011). It is thus conceivable that ciliary signaling is continuously required in mature neurons for the maintenance and modulation of neuronal network homeostasis. Moreover, the source and the molecular identity of the various environmental cues, including neurotransmitters or neuromodulators, that can initiate or modulate primary cilia signaling in mature neurons, and whether such signaling enables neurons to function cooperatively (Karnani et al., 2016) to modulate the dynamics of a circuit underlying specific functions or behavior are yet to be fully characterized. In this regard, the role of primary cilia signaling via ciliary melanocortin-4 receptors (MC4R) in hypothalamic neurons to regulate food intake and body weight provides an informative example (Siljee et al., 2018). Future efforts aimed at decisively resolving the above outlined issues will further our understanding of the fundamentally vital modulatory role primary cilia play in cerebral cortical formation, function, and disorders.

Acknowledgments

This research was supported by NIH grants MH060929 and NS to EA and the confocal imaging core of an NINDS institutional center core grant (5P30NS045892).

References

Akizu N, Cantagrel V, Schroth J, Cai N, Vaux K, McCloskey D, et al. (2013). AMPD2 regulates GTP synthesis and is mutated in a potentially treatable neurodegenerative brainstem disorder. Cell, 154(3), 505–517. 10.1016/j.cell.2013.07.005. [PubMed: 23911318]

Akizu N, Silhavy JL, Rosti RO, Scott E, Fenstermaker AG, Schroth J, et al. (2014). Mutations in CSPP1 lead to classical Joubert syndrome. American Journal of Human Genetics, 94(1), 80–86. 10.1016/j.ajhg.2013.11.015. [PubMed: 24360807]

Alvarez Retuerto AI, Cantor RM, Gleeson JG, Ustaszewska A, Schackwitz WS, Pennacchio LA, et al. (2008). Association of common variants in the Joubert syndrome gene (AHI1) with autism. Human Molecular Genetics, 17(24), 3887–3896. 10.1093/hmg/ddn291. [PubMed: 18782849]

Arellano JI, Guadiana SM, Breunig JJ, Rakic P, & Sarkisian MR (2017). Development and distribution of neuronal cilia in mouse neocortex. The Journal of Comparative Neurology, 520, 848–873. 10.1002/cne.22793.

Armato U, Chakravarthy B, Chiarini A, PrÃ ID, & Whitfield JF (2011). A paradigm-changing surprise from dentate gyrus granule cells—cilium-localized p75NTR may drive their

progenitor cell proliferation. Journal of Alzheimer's Disease & Parkinsonism, 1(2), 1–3. 10.4172/2161-0460.1000e104. e104.

Averaimo S, & Nicol X (2014). Intermingled cAMP, cGMP and calcium spatiotemporal dynamics in developing neuronal circuits. Frontiers in Cellular Neuroscience, 8, 376. 10.3389/fncel.2014.00376. [PubMed: 25431549]

Bakken TE, Miller JA, Ding SL, Sunkin SM, Smith KA, Ng L, et al. (2016). A comprehensive transcriptional map of primate brain development. Nature, 535(7612), 367–375. 10.1038/nature18637. [PubMed: 27409810]

Banker G (2018). The development of neuronal polarity: A retrospective view. International Journal of Neuroscience, 38, 1867–1873. United States: 2018 the authors 0270-6474/18/381867-07$15.00/0.

Baraban SC, Southwell DG,Estrada RC,Jones DL, Sebe JY, Alfaro-Cervello C, et al. (2009). Reduction of seizures by transplantation of cortical GABAergic interneuron precursors into Kv1.1 mutant mice. Proceedings of the National Academy of Sciences of the United States of America, 106, 15472–15477. [PubMed: 19706400]

Barnes AP, & Polleux F (2009). Establishment of axon-dendrite polarity in developing neurons. Annual Review of Neuroscience, 32, 347–381.

Basten SG, & Giles RH (2013). Functional aspects of primary cilia in signaling, cell cycle and tumorigenesis. Cilia, 2(1), 6. [PubMed: 23628112]

Baudoin J-P, Viou L, Launay P-S, Luccardini C, Espeso Gil S, Kiyasova V, et al. (2012). Tangentially migrating neurons assemble a primary cilium that promotes their reorientation to the cortical plate. Neuron, 76(6), 1108–1122. 10.1016/j.neuron.2012.10.027. [PubMed: 23259947]

Bhattarai SR (2015). Characteristics of primary cilia and centrosomes in neuronal and glial lineages of the adult brain. Denton, Texas: University of North Texas.

Bielas SL, Silhavy JL, Brancati F, Kisseleva MV, Al-Gazali L, Sztriha L, et al. (2009). Mutations in INPP5E, encoding inositol polyphosphate-5-phosphatase E, link phosphatidyl inositol signaling to the ciliopathies. Nature Genetics, 41(9), 1032–1036. [PubMed: 19668216]

Bilguvar K, Ozturk AK, Louvi A, Kwan KY, Choi M, Tatli B, et al. (2010). Whole-exome sequencing identifies recessive WDR62 mutations in severe brain malformations. Nature, 467(7312), 207–210. 10.1038/nature09327. [PubMed: 20729831]

Bishop GA, Berbari NF, Lewis J, & Mykytyn K (2007). Type III adenylyl cyclase localizes to primary cilia throughout the adult mouse brain. The Journal of Comparative Neurology, 505, 562–571. 10.1002/cne.21510. [PubMed: 17924533]

Bloodgood RA (2009). From central to rudimentary to primary: The history of an underappreciated organelle whose time has come. The primary cilium. Methods in Cell Biology, 94, 3–52. 10.1016/S0091-679X(08)94001-2. [PubMed: 20362083]

Bober MB, & Jackson AP (2017). Microcephalic osteodysplastic primordial dwarfism, type II: a clinical review. Current Osteoporosis Reports, 15(2), 61–69. 10.1007/s11914-017-0348-1. [PubMed: 28409412]

Boczek NJ, Hopp K, Benoit L, Kraft D, Cousin MA, Blackburn PR, et al. (2018). Characterization of three ciliopathy pedigrees expands the phenotype associated with biallelic C2CD3 variants. European Journal of Human Genetics, 26, 1797–1809. 10.18926/AMO/53020. [PubMed: 30097616]

Bond J, Roberts E, Mochida GH, Hampshire DJ, Scott S, Askham JM, et al. (2002). ASPM is a major determinant of cerebral cortical size. Nature Genetics, 32, 316–320. United States. [PubMed: 12355089]

Brancati F, Dallapiccola B, & Valente E (2010). Joubert syndrome and related disorders. Orphanet Journal of Rare Diseases, 5(1), 20. 10.1186/1750-1172-5-20. [PubMed: 20615230]

Breunig JJ, Sarkisian MR, Arellano JI, Morozov YM, Ayoub AE, Sojitra S, et al. (2008). Primary cilia regulate hippocampal neurogenesis by mediating sonic hedgehog signaling. Proceedings of the National Academy of Sciences of the United States of America, 105(35), 13127–13132. 10.1073/pnas.0804558105. [PubMed: 18728187]

Broix L, Asselin L, Silva CG, Ivanova EL, Tilly P, Gilet JG, et al. (2018). Ciliogenesis and cell cycle alterations contribute to KIF2A-related malformations of cortical development. Human Molecular

Genetics, 27, 224–238. England: The Author 2017. Published by Oxford University Press For Permissions, please journals.permissions@oup.com. [PubMed: 29077851]

Canning P, Park K, Goncalves J, Li C, Howard CJ, Sharpe TD, et al. (2018). CDKL family kinases have evolved distinct structural features and ciliary function. Cell Reports, 22(4), 885–894. 10.1016/j.celrep.2017.12.083. [PubMed: 29420175]

Caspary T, Larkins CE, & Anderson KV (2007). The graded response to sonic hedgehog depends on cilia architecture. Developmental Cell, 12, 767–778. United States. [PubMed: 17488627]

Cavallin M, Bijlsma EK, El Morjani A, Moutton S, Peeters EA, Maillard C, et al. (2017). Recurrent KIF2A mutations are responsible for classic lissencephaly. Neurogenetics, 18, 73–79. United States. [PubMed: 27747449]

Chattopadhyaya B, Di Cristo G, Higashiyama H, Knott GW, Kuhlman SJ, Welker E, et al. (2004). Experience and activity-dependent maturation of perisomatic GABAergic innervation in primary visual cortex during a postnatal critical period. Journal of Neuroscience, 24, 9598–9611. [PubMed: 15509747]

Chedotal A, & Richards LJ (2010). Wiring the brain: The biology of neuronal guidance. Cold Spring Harbor Perspectives in Biology, 2(6), a001917. 10.1101/cshperspect.a001917. [PubMed: 20463002]

Choi YJ, Di Nardo A, Kramvis I, Meikle L, Kwiatkowski DJ, Sahin M, et al. (2008). Tuberous sclerosis complex proteins control axon formation. Genes & Development, 22(18), 2485–2495. 10.1101/gad.1685008. [PubMed: 18794346]

Choi Y-H, Suzuki A, Hajarnis S, Ma Z, Chapin HC, Caplan MJ, et al. (2011). Polycystin-2 and phosphodiesterase 4C are components of a ciliary A-kinase anchoring protein complex that is disrupted in cystic kidney diseases. Proceedings of the National Academy of Sciences of the United States of America, 108(26), 10679–10684. 10.1073/pnas.1016214108. [PubMed: 21670265]

Christensen ST, Clement CA, Satir P, & Pedersen LB (2012). Primary cilia and coordination of receptor tyrosine kinase (RTK) signalling. The Journal of Pathology, 226(2), 172–184. 10.1002/path.3004. [PubMed: 21956154]

Christensen ST, Morthorst SK, Mogensen JB, & Pedersen LB (2017). Primary cilia and coordination of receptor tyrosine kinase (RTK) and transforming growth factor β (TGF-β) signaling. Cold Spring Harbor Perspectives in Biology. 10.1101/cshperspect.a028167.

Cionni JM, Wong HH-W, Bressan D, Kodama L, Harris WA, & Holt CE (2018). Axon-axon interactions regulate topographic optic tract sorting via CYFIP2-dependent WAVE complex function. Neuron, 97, 1078–1093. 10.1016/j.neuron.2018.01.027. [PubMed: 29518358]

Civelli O (2012). Orphan GPCRs and neuromodulation. Neuron, 76(1), 12–21. 10.1016/j.neuron.2012.09.009. [PubMed: 23040803]

Conduit SE, Dyson JM, & Mitchell CA (2012). Inositol polyphosphate 5-phosphatases; new players in the regulation of cilia and ciliopathies. FEBS Letters, 586(18), 2846–2857. 10.1016/j.febslet.2012.07.037. [PubMed: 22828281]

Courchet J, Lewis TL Jr., Lee S, Courchet V, Liou D-Y, Aizawa S, et al. (2013). Terminal axon branching is regulated by the LKB1-NUAK1 kinase pathway via presynaptic mitochondrial capture. Cell, 153(7), 1510–1525. 10.1016/j.cell.2013.05.021. [PubMed: 23791179]

DeCaen PG, Delling M, Vien TN, & Clapham DE (2015). Direct recording and molecular identification of the calcium channel of primary cilia. Nature, 504(7479), 315–318. 10.1038/nature12832.

Delgehyr N, & Spassky N (2014). Interplay between primary cilia and cell cycle. Medecine Sciences, 30, 976–979. France: 2014 medecine/sciences - Inserm. [PubMed: 25388579]

Delling M, DeCaen PG, Doerner JF, Febvay S, & Clapham DE (2013). Primary cilia are specialized calcium signalling organelles. Nature, 504, 311–314. [PubMed: 24336288]

Di Nardo A, & Sahin M (2018). mTOR'ing across the cortex by chopping the cilia. Neuron, 99(1), 3–5. 10.1016/j.neuron.2018.06.042. [PubMed: 30001510]

Dixon-Salazar T, Silhavy JL, Marsh SE, Louie CM, Scott LC, Gururaj A, et al. (2004). Mutations in the AHI1 gene, encoding jouberin, cause Joubert syndrome with cortical polymicrogyria. American Journal of Human Genetics, 75(6), 979–987. 10.1086/425985. [PubMed: 15467982]

Doherty D (2009). Joubert Syndrome: Insight into brain development, cilium biology, and complex disease. Seminars in Pediatric Neurology, 16(3), 144–154. 10.1016/j.spen.2009.06.002.

Ecker A (1844). Flimmerbewegung im Gehörorgan von Petromyzon marinus. Archiv für Anatomie, Physiologie und wissenschaftliche Medicin, 1, 520–521.

Engle EC (2010). Human genetic disorders of axon guidance. Cold Spring Harbor Perspectives in Biology, 2(3), a001784. 10.1101/cshperspect.a001784. [PubMed: 20300212]

Failler M, Gee H, Krug P,Joo K, Halbritter J, Belkacem L, et al. (2014).Mutations of CEP83 cause infantile nephronophthisis and intellectual disability. American Journal of Human Genetics, 94(6), 905–915. 10.1016/j.ajhg.2014.05.002. [PubMed: 24882706]

Falcon-Urrutia P, Carrasco CM, Lois P, Palma V, & Roth AD (2015). Shh signaling through the primary cilium modulates rat oligodendrocyte differentiation. PLoS One, 10(7). 10.1371/journal.pone.0133567.

Ferent J, Constable S, Gigante ED, Yam PT, Mariani LE, Legué E, et al. (2019). The ciliary protein Arl13b functions outside of the primary cilium in Shh-mediated axon guidance. Cell Reports, 29(11), 3356–3366.e3. 10.1016/j.celrep.2019.11.015. [PubMed: 31825820]

Ferland R, Eyaid W, Collura R, Tully L, Hill R, Al-Nouri D, et al. (2004). Abnormal cerebellar development and axonal decussation due to mutations in AHI1 in Joubert syndrome. Nature Genetics, 36(9), 1008–1013. 10.1038/ng1419. [PubMed: 15322546]

Fliegauf M, Benzing T, & Omran H (2007). When cilia go bad: Cilia defects and ciliopathies. Nature Reviews Molecular Cell Biology, 8, 880–893. England. [PubMed: 17955020]

Foerster P, Daclin M, Asm S, Faucourt M, Boletta A, Genovesio A, et al. (2017). mTORC1 signaling and primary cilia are required for brain ventricle morphogenesis. Development, 144(2), 201–210. 10.1242/dev.138271. [PubMed: 27993979]

Franco I, Gulluni F, Campa CC, Costa C, Margaria JP, Ciraolo E, et al. (2014). PI3K class II alpha controls spatially restricted endosomal PtdIns3P and Rab11 activation to promote primary cilium function. Developmental Cell, 28(6), 647–658. 10.1016/j.devcel.2014.01.022. [PubMed: 24697898]

Gabriel E, Wason A, Ramani A, Gooi LM, Keller P, Pozniakovsky A, et al. (2016). CPAP promotes timely cilium disassembly to maintain neural progenitor pool. The EMBO Journal, 35(8), 803–819. 10.15252/embj.201593679. [PubMed: 26929011]

Gavi S, Shumay E, Wang H.-y., & Malbon CC (2006). G-protein-coupled receptors and tyrosine kinases: Crossroads in cell signaling and regulation. Trends in Endocrinology & Metabolism, 17(2), 48–54. 10.1016/j.tem.2006.01.006. [PubMed: 16460957]

Geoffroy CG, Lorenzana AO, Kwan JP, Lin K, Ghassemi O, Ma A, et al. (2015). Effects of PTEN and nogo codeletion on corticospinal axon sprouting and regeneration in mice. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 35(16), 6413–6428. 10.1523/jneurosci.4013-14.2015. [PubMed: 25904793]

Gherman A, Davis EE, & Katsanis N (2006). The ciliary proteome database: An integrated community resource for the genetic and functional dissection of cilia. Nature Genetics, 38(9), 961–962. 10.1038/ng0906-961. [PubMed: 16940995]

Gibson DA, & Ma L (2011). Developmental regulation of axon branching in the vertebrate nervous system. Development, 138(2), 183–195. 10.1242/dev.046441. [PubMed: 21177340]

Green JA, & Mykytyn K (2014). neuronal primary cilia: an under appreciated signaling and sensory organelle in the brain. Neuropsychopharmacology, 39, 244–245. 10.1038/npp.2013.203. [PubMed: 24317320]

Grochowsky A, & Gunay-Aygun M (2019). Clinical characteristics of individual organ system disease in non-motile ciliopathies. Translational Science of Rare Diseases, 4(1-2), 1–23. 10.3233/TRD-190033. [PubMed: 31763176]

Guadiana SM, Semple-Rowland S, Daroszewski D, Madorsky I, Breunig JJ, Mykytyn K, et al. (2013). Arborization of dendrites by developing neocortical neurons is dependent on primary cilia and type 3 adenylyl cyclase. The Journal of Neuroscience, 33(6), 2626–2638. 10.1523/jneurosci.2906-12.2013. [PubMed: 23392690]

Guemez-Gamboa A, Coufal NG, & Gleeson JG (2014). Primary cilia in the developing and mature brain. Neuron, 82(3), 511–521. [PubMed: 24811376]

Guo J, Higginbotham H, Li J, Nichols J, Hirt J, Ghukasyan V, et al. (2015). Developmental disruptions underlying brain abnormalities in ciliopathies. Nature Communications, 6(7857). 10.1038/ncomms8857.

Guo J, Otis JM, Higginbotham H, Monckton C, Cheng J, Asokan A, et al. (2017). Primary cilia signaling shapes the development of interneuronal connectivity. Developmental Cell, 42(3), 286–300. e284. [PubMed: 28787594]

Guo J, Otis J, Suciu S, Catalano C, Xing L, Constable S, et al. (2019). Primary cilia signaling promotes axonal tract development and is disrupted in Joubert syndrome-related disorders models. Developmental Cell, 51, 759–774. 10.1016/j.devel.2019.11.005. [PubMed: 31846650]

Han YG, & Alvarez-Buylla A (2010). Role of primary cilia in brain development and cancer. Current Opinion in Neurobiology, 20(1), 58–67. 10.1016/j.conb.2009.12.002. [PubMed: 20080044]

Han YG, Kim HJ, Dlugosz AA, Ellison DW, Gilbertson RJ, & Alvarez-Buylla A (2009). Dual and opposing roles of primary cilia in medulloblastoma development. Nature Medicine, 15(9), 1062–1065. 10.1038/nm.2020.

Harwell CC, Parker PR, Gee SM, Okada A, McConnell SK, Kreitzer AC, et al. (2012). Sonic hedgehog expression in corticofugal projection neurons directs cortical microcircuit formation. Neuron, 73(6), 1116–1126. 10.1016/j.neuron.2012.02.009. [PubMed: 22445340]

Hayashi S, Inoue Y, Kiyonari H, Abe T, Misaki K, Moriguchi H, et al. (2014). Protocadherin-17 mediates collective axon extension by recruiting actin regulator complexes to interaxonal contacts. Developmental Cell, 30(6), 673–687. 10.1016/j.devcel.2014.07.015. [PubMed: 25199687]

Henle SJ, Wang G, Liang E, Wu M, Poo M.m., & Henley JR (2011). Asymmetric PI(3,4,5)P3 and Akt signaling mediates chemotaxis of axonal growth cones. Journal of Neuroscience, 31(19), 7016–7027. 10.1523/jneurosci.0216-11.2011. [PubMed: 21562263]

Higginbotham H, Eom TY, Mariani LE, Bachleda A, Hirt J, Gukassyan V, et al. (2012). Arl13b in primary cilia regulates the migration and placement of interneurons in the developing cerebral cortex. Developmental Cell, 23(5), 925–938. [PubMed: 23153492]

Higginbotham H, Guo J, Yokota Y, Umberger N, Su C, Li J, et al. (2013). Arl13b-regulated cilia activities are essential for polarized radial glial scaffold formation. Nature Neuroscience, 16(8), 1000–1007. 10.1038/nn.3451. [PubMed: 23817546]

Hildebrandt F, Benzing T, & Katsanis N (2011). Ciliopathies. The New England Journal of Medicine, 364(16), 1533–1543. 10.1056/nejmra1010172. [PubMed: 21506742]

Hilgendorf KI, Johnson CT, & Jackson PK (2016). The primary cilium as a cellular receiver: organizing ciliary GPCR signaling. Current Opinion in Cell Biology, 39, 84–92. 10.1016/j.ceb.2016.02.008. [PubMed: 26926036]

Hoshina N, Tanimura A, Yamasaki M, Inoue T, Fukabori R, Kuroda T, et al. (2013). Protocadherin 17 regulates presynaptic assembly in topographic corticobasal ganglia circuits. Neuron, 78(5), 839–854. 10.1016/j.neuron.2013.03.031. [PubMed: 23684785]

Huang WC, Chen Y, & Page DT (2016). Hyperconnectivity of prefrontal cortex to amygdala projections in a mouse model of macrocephaly/autism syndrome. Nature Communications, 7. 10.1038/ncomms13421, 13421.

Ishikawa H, Thompson J, Yates JR 3rd, & Marshall WF (2012). Proteomic analysis of mammalian primary cilia. Current Biology, 22(5), 414–419. 10.1016/j.cub.2012.01.031. [PubMed: 22326026]

Jacoby M, Cox JJ, Gayral S, Hampshire DJ, Ayub M, Blockmans M, et al. (2009). INPP5E mutations cause primary cilium signaling defects, ciliary instability and ciliopathies in human and mouse. Nature Genetics, 41(9), 1027–1031. 10.1038/ng.427. [PubMed: 19668215]

Jissendi-Tchofo P, Severino M, Nguema-Edzang B, Toure C, Soto Ares G, & Barkovich AJ (2015). Update on neuroimaging phenotypes of mid-hindbrain malformations. Neuroradiology, 57(2), 113–138. 10.1007/s00234-014-1431-2. [PubMed: 25339235]

Juric-Sekhar G, Adkins J, Doherty D, & Hevner RF (2012). Joubert syndrome: Brain and spinal cord malformations in genotyped cases and implications for neurodevelopmental functions of primary cilia. Acta Neuropathologica, 123(5), 695–709. 10.1007/s00401-012-0951-2. [PubMed: 22331178]

Kalil K, & Dent EW (2014). Branch management: mechanisms of axon branching in the developing vertebrate CNS. Nature Reviews. Neuroscience, 15(1), 7–18. 10.1038/nrn3650. [PubMed: 24356070]

Kalil K, Li L, & Hutchins BI (2011). Signaling mechanisms in cortical axon growth, guidance and branching. Frontiers in Neuroanatomy, 5, 62. 10.3389/fnana.2011.00062. [PubMed: 22046148]

Karnani MM, Jackson J, Ayzenshtat I, Tucciarone J, Manoocheri K, Snider WG, et al. (2016). Cooperative subnetworks of molecularly similar interneurons in mouse neocortex. Neuron, 90(1), 86–100. 10.1016/j.neuron.2016.02.037. [PubMed: 27021171]

Kasahara K, Miyoshi K, Murakami S, Miyazaki I, & Asanuma M (2014). Visualization of astrocytic primary cilia in the mouse brain by immunofluorescent analysis using the cilia marker Arl13b. Acta Medica Okayama, 68(6), 317–322. 10.18926/AMO/53020. [PubMed: 25519025]

Keryer G, Pineda JR, Liot G, Kim J, Dietrich P, Benstaali C, et al. (2011). Ciliogenesis is regulated by a huntingtin-HAP1-PCM1 pathway and is altered in Huntington disease. The Journal of Clinical Investigation, 121(11), 4372–4382. 10.1172/JCI57552. [PubMed: 21985783]

Kheradmand Kia S, Verbeek E, Engelen E, Schot R, Poot RA, de Coo IF, et al. (2012). RTTN mutations link primary cilia function to organization of the human cerebral cortex. American Journal of Human Genetics, 91(3), 533–540. 10.1016/j.ajhg.2012.07.008. [PubMed: 22939636]

Kohli P, Höhne M,Jüngst C, Bertsch S, Ebert LK, Schauss AC, et al. (2017). The ciliary membrane-associated proteome reveals actin-binding proteins as key components of cilia. EMBO Reports, 18(9), 1521–1535. 10.15252/embr.201643846. [PubMed: 28710093]

Kolliker A (1854). Manual of human microscopical anatomy (translation by George Busk of Mikroskopische Anatomie). Philadelphia: Lippincott: Grambo and Company.

Kowalevsky A (1867). Entwickelungsgeschichte des *Amphioxus lanceolatus*. Memoires de l'Academie Imperiale des Sciences de St-Petersbourg (ser VII), 11, 1–17.

Kumamoto N, Gu Y, Wang J, Janoschka S, Takemaru K-I, Levine J, et al. (2012). A role for primary cilia in glutamatergic synaptic integration of adult-born neurons. Nature Neuroscience, 15(3), 399–405. 10.1038/nn.3042. [PubMed: 22306608]

Kwan K, Sestan N, & Anton E (2012). Transcriptional co-regulation of neuronal migration and laminar identity in the neocortex. Development, 139(9), 1535–1546. 10.1242/dev.069963. [PubMed: 22492350]

Kwon C-H, Luikart BW, Powell CM, Zhou J, Matheny SA, Zhang W, et al. (2006). Pten regulates neuronal arborization and social interaction in mice. Neuron, 50(3), 377–388. 10.1016/j.neuron.2006.03.023. [PubMed: 16675393]

Laclef C, Anselme I, Besse L, Catala M, Palmyre A, Baas D,et al. (2015). The role of primary cilia in corpus callosum formation is mediated by production of the Gli3 repressor. Human Molecular Genetics, 24(17), 4997–5014. 10.1093/hmg/ddv221. [PubMed: 26071364]

Lancaster MA, & Gleeson JG (2009). The primary cilium as a cellular signaling center: Lessons from disease. Current Opinion in Genetics & Development, 19, 220–229. 10.1016/J.GDE.2009.04.008. [PubMed: 19477114]

Langerhans P (1876). Zur Anatomie des Amphioxus. Archiv für Mikroskopische Anatomie, 12, 290–348.

Lehtinen MK, Zappaterra MW, Chen X, Yang YJ, Hill AD, Lun M, et al. (2011). The cerebrospinal fluid provides a proliferative niche for neural progenitor cells. Neuron, 69(5), 893–905. 10.1016/j.neuron.2011.01.023. [PubMed: 21382550]

Lemmon MA, & Schlessinger J (2010). Cell signaling by receptor tyrosine kinases. Cell, 141(7), 1117–1134. 10.1016/j.cell.2010.06.011. [PubMed: 20602996]

Lepanto P, Badano JL, & Zolessi FR (2016). Neuron's little helper: The role of primary cilia in neurogenesis. Neurogenesis, 3(1). 10.1080/23262133.2016.1253363, e1253363. [PubMed: 28090545]

Lesiak AJ, Brodsky M, Cohenca N, Croicu AG, & Neumaier JF (2018). Restoration of physiological expression of 5-HT6 receptor into the primary cilia of null mutant neurons lengthens both primary cilia and dendrites. Molecular Pharmacology, 94(1), 731–742. 10.1124/mol.117.111583. [PubMed: 29678909]

Li A, Saito M, Chuang JZ, Tseng YY, Dedesma C, Tomizawa K, et al. (2011). Ciliary transition zone activation of phosphorylated Tctex-1 controls ciliary resorption, S-phase entry and fate of neural progenitors. Nature Cell Biology, 13(4), 402–411. 10.1038/ncb2218. [PubMed: 21394082]

Loo L, Simon JM, Xing L, McCoy ES, Niehaus JK, Guo J, et al. (2019). Single-cell transcriptomic analysis of mouse neocortical development. Nature Communications, 10(1), 134.

Mardinly AR, Spiegel I, Patrizi A, Centofante E, Bazinet JE, Tzeng CP, et al. (2016). Sensory experience regulates cortical inhibition by inducing IGF1 in VIP neurons. Nature, 531(7594), 371–375. 10.1038/nature17187. [PubMed: 26958833]

Marley A, & von Castro M (2012). A simple cell-based assay reveals that diverse neuropsychiatric risk genes converge on primary cilia. PLoS One, 7. 10.1371/journal.pone.0046647.

Marley A, & von Zastrow M (2010). DISC1 regulates primary cilia that display specific dopamine receptors. PLoS One, 5(5). 10.1371/journal.pone.0010902, e10902. [PubMed: 20531939]

Matsumoto M, Sawada M, García-González D, Herranz-Pérez V, Ogino T, Bang Nguyen H, et al. (2019). Dynamic changes in ultrastructure of the primary cilium in migrating neuroblasts in the postnatal brain. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 39(50), 9967–9988. 10.1523/JNEUROSCI.1503-19.2019. [PubMed: 31685650]

Mattila PK, & Lappalainen P (2008). Filopodia: molecular architecture and cellular functions. Nature Reviews. Molecular Cell Biology, 9(6), 446–454. 10.1038/nrm2406. [PubMed: 18464790]

McIntyre JC, Davis EE, Joiner A, Williams CL, Tsai IC, Jenkins PM, et al. (2012). Gene therapy rescues cilia defects and restores olfactory function in a mammalian ciliopathy model. Nature Medicine, 18, 1423–1428. 10.1038/nm.2860.

Mejillano MR, Kojima S, Applewhite DA, Gertler FB, Svitkina TM, & Borisy GG (2004). Lamellipodial versus filopodial mode of the actin nanomachinery: Pivotal role of the filament barbed end. Cell, 118(3), 363–373. 10.1016/j.cell.2004.07.019. [PubMed: 15294161]

Mick DU, Rodrigues RB, Leib RD, Adams CM, Chien AS, Gygi SP, et al. (2015). Proteomics of primary cilia by proximity labeling. Developmental Cell, 35(4), 497–512. [PubMed: 26585297]

Mitchison H, & Valente E (2017). Motile and non-motile cilia in human pathology: From function to phenotypes. Journal of Pathology, 241, 294–309. 10.1002/path.4843.

Miyoshi K, Kasahara K, Miyazaki I, & Asanuma M (2009). Lithium treatment elongates primary cilia in the mouse brain in in cultured cells. Biochemical and Biophysical Research Communications, 388, 757–762. 10.1016/j.bbrc.2009.08.099. [PubMed: 19703416]

Molnár Z, Clowry GJ, Šestan N, Alzu'bi A, Bakken T, Hevner RF, et al. (2019). New insights into the development of the human cerebral cortex. Journal of Anatomy, 235, 432–451. 10.1111/joa.13055. [PubMed: 31373394]

Monuki E, & Walsh C (2001). Mechanisms of cerebral cortical patterning in mice and humans. Nature Neuroscience, 4, 1199–1206. 10.1038/nn752.

Moser JJ, Fritzler MJ, & Rattner JB (2009). Primary ciliogenesis defects are associated with human astrocytoma/glioblastoma cells. BMC Cancer, 9(448). 10.1186/1471-2407-9-448.

Mukhopadhyay S, & Rohatgi R (2014). G-protein-coupled receptors, Hedgehog signaling and primary cilia. Seminars in Cell and Developmental Biology, 33, 63–72. 10.1016/j.semcdb.2014.05.002. [PubMed: 24845016]

Muñoz-Estrada J, Lora-Castellanos A, Meza I, Alarcón Elizaldes S, & Benítez-King G (2017). Primary cilia formation is diminished in schizophrenia and bipolar disorder: A possible marker for these psychiatric diseases. Schizophrenia Research, 195, 412–420. 10.1016/j.schres.2017.08.055. [PubMed: 28927861]

Nager AR, Goldstein JS, Herranz-Perez V, Portran D, Ye F, Garcia-Verdugo JM, et al. (2017). An actin network dispatches ciliary GPCRs into extracellular vesicles to modulate signaling. Cell, 168, 252–263. [PubMed: 28017328]

Nanni L, Ming JE, Bocian M, Steinhaus K, Bianchi DW, Die-Smulders C, et al. (1999). The mutational spectrum of the sonic hedgehog gene in holoprosencephaly: SHH mutations cause a significant proportion of autosomal dominant holoprosencephaly. Human Molecular Genetics, 8, 2479–2488. England. [PubMed: 10556296]

Narita K, Kozuka-Hata H, Nonami Y, et al. (2012). Proteomic analysis of multiple primary cilia reveals a novel mode of ciliary development in mammals. Biology Open, 1(8), 815–825. 10.1242/bio.20121081. [PubMed: 23213475]

Nechipurenko IV, Doroquez DB, & Sengupta P (2013). Primary cilia and dendritic spines: Different but similar signaling compartments. Molecules and Cells, 36(4), 288–303. 10.1007/s10059-013-0246-z. [PubMed: 24048681]

Nicholas AK, Khurshid M, Desir J, Carvalho OP, Cox JJ, Thornton G, et al. (2010). WDR62 is associated with the spindle pole and is mutated in human microcephaly. Nature Genetics, 42(11), 1010–1014. 10.1038/ng.682. [PubMed: 20890279]

Nichols AS, Floyd DH,Bruinsma SP, Narzinski K, & Baranski TJ (2013). Frizzled receptors signal through G proteins. Cellular Signalling, 25(6), 1468–1475. 10.1016/j.cellsig.2013.03.009. [PubMed: 23524329]

Nishikimi M, Oishi K, & Nakajima K (2013). Axon guidance mechanisms for establishment of callosal connections. Neural Plasticity, 2013(2), 1–7. 10.1155/2013/149060.

Novarino G, Akizu N, & Gleeson JG (2011). Modeling human disease in humans: The ciliopathies. Cell, 147(1), 70–79. 10.1016/j.cell.2011.09.014. [PubMed: 21962508]

Omori Y, Chaya T, Yoshida S, Irie S,Tsujii T, & Furukawa T (2015). Identification of G protein-coupled receptors (GPCRs) in primary cilia and their possible involvement in body weight control. PLoS One, 10(6). 10.1371/journal.pone.0128422. e0128422–0128417. [PubMed: 26053317]

Pablo JL, DeCaen PG, & Clapham DE (2017). Progress in ciliary ion channel physiology. The Journal of General Physiology, 149, 37–47. 10.1085/jgp.20161169. [PubMed: 27999145]

Paolino A, Fenlon LR, Suárez R, & Richards LJ (2018). Transcriptional control of long-range cortical projections. Current Opinion in Neurobiology, 53, 57–65. 10.1016/j.conb.2018.05.005. [PubMed: 29894898]

Parisi MA (2009). Clinical and molecular features of Joubert syndrome and related disorders. American Journal of Medical Genetics. Part C, Seminars in Medical Genetics, 151C(4), 326–340. 10.1002/ajmg.c.30229.

Parisi MA (2019). The molecular genetics of Joubert syndrome and related ciliopathies: The challenges of genetic and phenotypic heterogeneity. Translational Science of Rare Diseases, 4, 25–49. 10.3233/TRD-190041. [PubMed: 31763177]

Park SM, Jang HJ, & Lee JH (2019). Roles of primary cilia in the developing brain. Frontiers of Cellular Neuroscience, 13(218). 10.3389/fncel.2019.00218.

Park S, Lim J, Ramakrishina S, Kim S, Kim W, Lee J, et al. (2018). Brain somatic mutations in MTOR disrupt neuronal ciliogenesis, Leading to focal cortical dyslamination. Neuron, 99(1), 83–97. 10.1016/j.neuron.2018.05.039. [PubMed: 29937275]

Parra LM, & Zou Y (2010). Sonic hedgehog induces response of commissural axons to Semaphorin repulsion during midline crossing. Nature Neuroscience, 13, 29–35. United States. [PubMed: 19946319]

Phua SC, Lin Y-C, & Inoue T (2015). An intelligent nano-antenna: Primary cilium harnesses TRP channels to decode polymodal stimuli. Cell Calcium, 58(4), 415–422. 10.1016/j.ceca.2015.03.005. [PubMed: 25828566]

Poduri A, Evrony GD, Cai X, Elhosary PC, Beroukhim R, Lehtinen MK, et al. (2012). Somatic activation of AKT3 causes hemispheric developmental brain malformations. Neuron, 74(1), 41–48. 10.1016/j.neuron.2012.03.010. [PubMed: 22500628]

Poirier K, Lebrun N, Broix L, Tian G, Saillour Y, Boscheron C, et al. (2013). Mutations in TUBG1, DYNC1H1, KIF5C and KIF2A cause malformations of cortical development and microcephaly. Nature Genetics, 45(6), 639–647. 10.1038/ng.2613. [PubMed: 23603762]

Poretti A, Boltshauser E, Loenneker T, Valente EM, Brancati F, Il'yasov K, et al. (2007). Diffusion tensor imaging in Joubert syndrome. American Journal of Neuroradiology, 28(10), 1929–1933. 10.3174/ajnr.A0703. [PubMed: 17898198]

Poretti A, Huisman TA, Scheer I, & Boltshauser E (2011). Joubert syndrome and related disorders: Spectrum of neuroimagingfindings in 75 patients. American Journal of Neuroradiology, 32(8), 1459–1463. 10.3174/ajnr.A2517. [PubMed: 21680654]

Puram SV, Kim AH, Ikeuchi Y, Wilson-Grady JT, Merdes A, Gygi SP, et al. (2011). A CaMKIIbeta signaling pathway at the centrosome regulates dendrite patterning in the brain. Nature Neuroscience, 14(8), 973–983. 10.1038/nn.2857. [PubMed: 21725312]

Putoux A, Baas D, Paschaki M, Morlé L, Maire C, Attié-Bitach T, et al. (2019). Altered GLI3 and FGF8 signaling underlies acrocallosal syndrome phenotypes in Kif7 depleted mice. Human Molecular Genetics, 28(6), 877–887. 10.1093/hmg/ddy392. [PubMed: 30445565]

Putoux A, Thomas S, Coene KL, Davis EE, Alanay Y, Ogur G, et al. (2011). KIF7 mutations cause fetal hydrolethalus and acrocallosal syndromes. Nature Genetics, 43(6), 601–606. 10.1038/ng.826. [PubMed: 21552264]

Qian X, Song H, & Ming GL (2019). Brain organoids: Advances, applications and challenges. Development, 146(8).

Raper J, & Mason C (2010). Cellular strategies of axonal pathfinding. Cold Spring Harbor Perspectives in Biology, 2(9), a001933. 10.1101/cshperspect.a001933. [PubMed: 20591992]

Reiter JF, & Leroux MR (2017). Genes and molecular pathways underpinning ciliopathies. Nature Reviews. Molecular Cell Biology, 18(9), 533–547. 10.1038/nrm.2017.60. [PubMed: 28698599]

Ringers C, Olstad EW, & Jurisch-Yaksi N (2020). The role of motile cilia in the development and physiology of the nervous system. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 375(1792), 20190156. 10.1098/rstb.2019.0156. [PubMed: 31884916]

Romani M, Micalizzi A, & Valente EM (2013). Joubert syndrome: Congenital cerebellar ataxia with the molar tooth. The Lancet Neurology, 12(9), 894–905. 10.1016/S1474-4422(13)70136-4. [PubMed: 23870701]

Sanchez MA, & Armstrong RC (2018). Postnatal sonic hedgehog (Shh) responsive cells give rise to oligodendrocyte lineage cells during myelination and in adulthood contribute to remyelination. Experimental Neurology, 299, 122–136. United States: Published by Elsevier Inc. [PubMed: 29045809]

Sarkisian MR, & Guadiana SM (2015). Influences of primary cilia on cortical morphogenesis and neuronal subtype maturation. Neuroscience, 21, 136–151. 10.1177/1073858414531074.

Sarkisian MR, & Semple-Rowland SL (2019). Emerging roles of primary cilia in glioma. Frontiers in Cellular Neuroscience, 13(55). 10.3389/fncel.2019.00055.

Sattar S, & Gleeson JG (2011). The ciliopathies in neuronal development: a clinical approach to investigation of Joubert syndrome and Joubert syndrome-related disorders. Developmental Medicine and Child Neurology, 53, 793–798. 10.1111/j.1469-8749.2011.04021.x. [PubMed: 21679365]

Schneider JW, Gao Z, Li S, Farooqi M, Tang TS, Bezprozvanny I, et al. (2008). Small-molecule activation of neuronal cell fate. Nature Chemical Biology, 4(7), 408–410. 10.1038/nchembio.95. [PubMed: 18552832]

Schou KB, Pedersen LB, & Christensen ST (2015). Ins and outs of GPCR signaling in primary cilia. EMBO Reports, 16(9), 1099–1113. 10.15252/embr.201540530. [PubMed: 26297609]

Seeger-Nukpezah T, & Golemis EA (2012). The extracellular matrix and ciliary signaling. Current Opinion in Cell Biology, 24(5), 652–661. 10.1016/j.ceb.2012.06.002. [PubMed: 22819513]

Sengupta P (2017). Cilia and sensory signaling: The journey from “animalcules” to human disease. PLoS Biology, 15, e2002240. [PubMed: 28410391]

Senocak EU, Oguz KK, Haliloglu G, Topcu M, & Cila A (2010). Structural abnormalities of the brain other than molar tooth sign in Joubert syndrome-related disorders. Diagnostic and Interventional Radiology, 16(1), 3–6. 10.4261/1305-3825.DIR.2673-09.1. [PubMed: 20108204]

Shamseldin H, Alazami AM, Manning M, Hashem A, Caluseiu O, Tabarki B, et al. (2015). RTTN mutations cause primary microcephaly and primordial dwarfism in humans. American Journal of Human Genetics, 97(6), 862–868. 10.1016/j.ajhg.2015.10.012. [PubMed: 26608784]

Shao W, Yang J, He M, Yu XY, Lee CH, Yang Z, et al. (2020). Centrosome anchoring regulates progenitor properties and cortical formation. Nature, 580(7801), 106–112. 10.1038/s41586-020-2139-6. [PubMed: 32238932]

Shin J, Kim M, Jung H-J, Cha HL, Suh-Kim H, Ahn S, et al. (2017). Characterization of developmental defects in the forebrain resulting from hyperactivated mTOR signaling by

integrative analysis of transcriptomic and proteomic data. Scientific Reports, 7(1), 2826. 10.1038/s41598-017-02842-6. [PubMed: 28588230]

Shohayeb B, Ho U, Yeap YY, Parton RG, Millard SS, Xu Z, et al. (2020). The association of microcephaly protein WDR62 with CPAP/IFT88 is required for cilia formation and neocortical development. Human Molecular Genetics, 29, 248–263. England: The Author(s) 2019. Published by Oxford University Press For Permissions, please journals.permissions@oup.com. [PubMed: 31816041]

Sigg MA, Menchen T, Lee C, Johnson J, Jungnickel MK, Choksi SP, et al. (2017). Evolutionary proteomics uncovers ancient associations of cilia with signaling pathways. Developmental Cell, 43(6), 744–762.e11. 10.1016/j.devcel.2017.11.014. [PubMed: 29257953]

Siljee JE, Wang Y, Bernard AA, Ersoy BA, Zhang S, Marley A, et al. (2018). Subcellular localization of MC4R with ADCY3 at neuronal primary cilia underlies a common pathway for genetic predisposition to obesity. Nature Genetics, 50, 180–185. 10.1038/s41588-017-0020-9. [PubMed: 29311635]

Southwell DG, Froemke RC, Alvarez-Buylla A, Stryker MP, & Gandhi SP (2010). Cortical plasticity induced by inhibitory neuron transplantation. Science, 327(5969), 1145–1148. 10.1126/science.1183962. [PubMed: 20185728]

Sterpka A, Yang J, Strobel M, Zhou Y, Pauplis C,& Chen X (2020). Diverged morphology changes of astrocytic and neuronal primary cilia under reactive insults. Molecular Brain, 13, 28. 10.1186/s13041-020-00571-y. [PubMed: 32122360]

Stoufflet J, Chaulet M, Doulazmi M, Fouquet C, Dubacq C, Métin C, et al. (2019). Primary cilium-dependent cAMP/PKA signaling at the centrosome regulates neuronal migration. BioRxiv. 10.1101/765925.

Suizu F, Hirata N, Kimura K, Edamura T, Tanaka T, Ishigaki S, et al. (2016). Phosphorylation-dependent Akt-inversin interaction at the basal body of primary cilia. The EMBO Journal, 35(12), 1346–1363. 10.15252/embj.201593003. [PubMed: 27220846]

Thauvin-Robinet C, Lee JS, Lopez E, Herranz-Perez V, Shida T, Franco B, et al. (2014). The oral-facial-digital syndrome gene C2CD3 encodes a positive regulator of centriole elongation. Nature Genetics, 46(8), 905–911. 10.1038/ng.3031. [PubMed: 24997988]

Thauvin-Robinet C, Thomas S, Sinico M, Aral B, Burglen L, Gigot N, et al. (2013). OFD1 mutations in males: phenotypic spectrum and ciliary basal body docking impairment. Clinical Genetics, 84(1), 86–90. 10.1111/cge.12013. [PubMed: 23036093]

Thion M, Ginhoux F, & Garel S (2018). Microglia and early brain development: An intimate journey. Science, 362(6411), 185–189. 10.1126/science.aat0474. [PubMed: 30309946]

Thomas S, Boutaud L, Reilly ML, & Benmerah A (2019). Cilia in hereditary cerebral anomalies. Biology of the Cell, 111, 217–231. 10.1111/boc.201900012. [PubMed: 31177551]

Thomas S, Legendre M, Saunier S, Bessieres B, Alby C, Bonniere M, et al. (2012). TCTN3 mutations cause Mohr-Majewski syndrome. American Journal of Human Genetics, 91(2), 372–378. 10.1016/j.ajhg.2012.06.017. [PubMed: 22883145]

Tong CK, Han Y-G, Shah JK, Obernier K, Guinto CD, & Alvarez-Buylla A (2014). Primary cilia are required in a unique subpopulation of neural progenitors. Proceedings of the National Academy of Sciences of the United States of America, 111, 12438–12443. 10.1073/pnas.1321425111. [PubMed: 25114218]

Tsai P, & Sahin M (2011). Mechanisms of neurocognitive dysfunction and therapeutic considerations in tuberous sclerosis complex. Current Opinion in Neurology, 24(2), 106–113. 10.1097/WCO.0b013e32834451c4. [PubMed: 21301339]

Uzquiano A, Cifuentes-Diaz C, Jabali A, Romero DM, Houllier A, Dingli F, et al. (2019). Mutations in the heterotopia gene Eml1/EML1 severely disrupt the formation of primary cilia. Cell Reports, 28, 1596–1611. 10.1016/j.celrep.2019.06.096. [PubMed: 31390572]

Valente EM, Rosti RO, Gibbs E, & Gleeson JG (2014). Primary cilia in neurodevelopmental disorders. Nature Reviews. Neurology, 10(1), 27–36. [PubMed: 24296655]

van Dam T, Kennedy J, van der Lee R, de Vrieze E, Wunderlich KA, Rix S, et al. (2019). CiliaCarta: An integrated and validated compendium of ciliary genes. PLoS One, 14(5), e0216705. 10.1371/journal.pone.0216705. [PubMed: 31095607]

van Dam TJ, Wheway G, Slaats GG, SYSCILIA Study Group, Huynen MA, & Giles RH (2013). The SYSCILIA gold standard (SCGSv1) of known ciliary components and its applications within a systems biology consortium. Cilia, 2(1), 7. 10.1186/2046-2530-2-7. [PubMed: 23725226]

Wang L, & Marquardt T (2013). What axons tell each other: Axon-axon signaling in nerve and circuit assembly. Current Opinion in Neurobiology, 23(6), 974–982. 10.1016/j.conb.2013.08.004. [PubMed: 23973157]

Wang X, Tsai JW, Imai JH, Lian WN, Vallee RB, & Shi SH (2009). Asymmetric centrosome inheritance maintains neural progenitors in the neocortex. Nature, 461(7266), 947–955. 10.1038/nature08435. [PubMed: 19829375]

Ware S, Gunay-Aygun M, & Hildebrandt F (2011). Spectrum of clinical diseases caused by disorders of primary cilia. Proceedings of the American Thoracic Society, 8, 444–450. 10.1513/pats.201103-025SD. [PubMed: 21926397]

Yokota Y, Ghashghaei H, Han C, Watson H, Campbell K, & Anton E (2007). Radial glial dependent and independent dynamics of interneuronal migration in the developing cerebral cortex. PLoS One, 2(8), 794. 10.1371/journal.pone.0000794.

Yu TW, & Bargmann CI (2001). Dynamic regulation of axon guidance. Nature Neuroscience, 4(Supp), 1169–1176. 10.1038/nn748.

Zhang W, Yang SL, Yang M, Herrlinger S, Shao Q, Collar JL, et al. (2019). Modeling microcephaly with cerebral organoids reveals a WDR62-CEP170-KIF2A pathway promoting cilium disassembly in neural progenitors. Nature Communications, 10(1), 2612. 10.1038/s41467-019-10497-2.

Zheng JQ, & Poo MM (2007). Calcium signaling in neuronal motility. Annual Review of Cell and Developmental Biology, 23, 375–404. 10.1146/annurev.cellbio.23.090506.123221.

Zhu D, Shi S, Wang H, & Liao K (2009). Growth arrest induces primary-cilium formation and sensitizes IGF-1-receptor signaling during differentiation induction of 3T3-L1 preadipocytes. Journal of Cell Science, 122(15), 2760–2768. 10.1242/jcs.046276. [PubMed: 19596798]

Zimmermann KW (1898). Beitrage zur Kenntniss einiger Drusen und Epithelien. Arch. Mikrosk. Anat, 52, 552–70610.

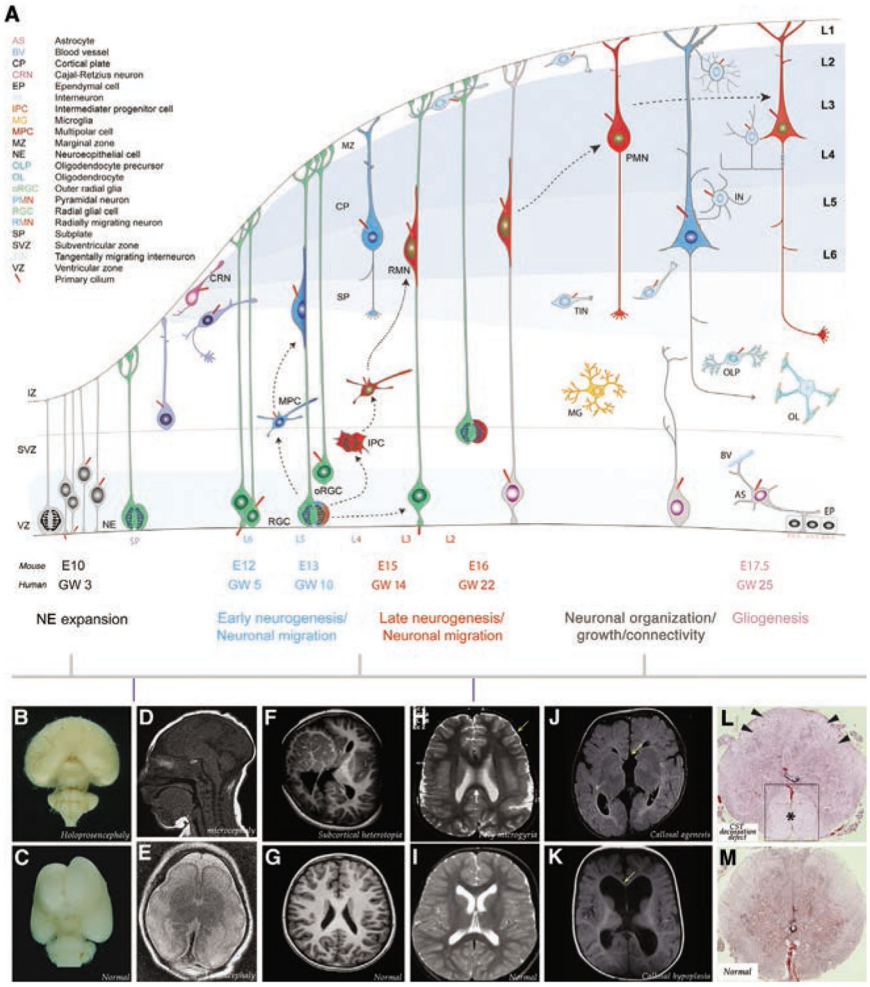

Fig. 1.

Development of the cerebral cortex and cortical malformations associated with primary ciliary dysfunction. (A) During early development, symmetrically dividing neuroepithelial cells (NPs) in the ventricular zone (VZ;blue) assume radial glial identity. Radial glia cells (RGCs) divide symmetrically to expand the RGC pool or asymmetrically to generate neurons and other progenitors (intermediate progenitor cells [IPCs] or outer radial glial cells [oRGC]). Newborn neurons assume a multipolar morphology and then migrate away from the germinal zones, guided by the basal processes of the RGCs, to reach the mantle layers. The first-born neurons settle within the preplate (PP) to form the nascent cortical plate (CP). Continued addition of subsequently generated neurons then split the PP into the marginal zone (MZ) and the subplate (SP), leading to sequential formation of deep (L6 and L5; blue) and upper layers (L4, L3 and L2; red) neurons of the cerebral cortex. Intermediate progenitor cells (IPCs) or outer radial glial cells (oRGC) derived from radial glia undergo symmetric neurogenic divisions in the SVZ to generate upper layer neurons. Concurrent to radial migration of projection neurons, tangentially migrating interneurons originating in the ganglionic eminence invade the cortical plate. At the end of neurogenesis, the radial glial scaffold is dismantled, progenitors become gliogenic, generate cortical and subependymal zone (SEZ) astrocytes (Ast), and give rise to a layer of ependymal

cells (EL). Early embryonic microglial (MG) invasion into the developing cerebral wall and oligodendrocyte precursor (OLP) generation and differentiation into oligodendrocytes (OL) are not illustrated. AS, astrocyte; BV, blood vessel; CP, cortical plate; CRN, Cajal-Retzius neuron; EP, ependymal cell; IN, interneuron; IPC, intermediate progenitor cell; MG, microglia; MPC, multipolar cell; MZ, marginal zone; NPC, neuroepithelial progenitor cell; OLP, oligodendrocyte precursor; OL, oligodendrocyte; oRGC, outer radial glia; PMN, Pyramidal neuron; RGC, radial glial cell, RMN, radially migrating neuron; SP, subplate; SVZ, subventricular zone, TIN, tangentially migrating interneuron; VZ, ventricular zone. A timeline of mouse embryonic (E) day or human gestational week (GW) relevant to the initial stages of the respective developmental events are indicated. (B–M) Primary cilia dysfunction during distinct stages of cortical development contributes to specific cortical malformations. (B, C) Shh mutations, likely disrupting cilia mediated Shh signaling, in NPs lead to holoprosencephaly. (D–G) Primary cilia malfunction in RGCs or migrating neurons can promote microcephaly (D), lissencephaly (E), and subcortical heterotopia (F, G). Primary cilia dysfunction in postmigratory neurons contributes to poly microgyria (H[arrow], I), callosal agenesis (arrow, J) or hypoplasia (arrow, K), and CST decussation defects (L, M [asterisk in boxed area indicates enlarged, nondecussating anterior CST in HE stained cervical spinal cord]). Images are reproduced from Monuki and Walsh (2001) (B, C), Shamseldin et al. (2015) (D, E; *RTTN* mutation), Uzquiano et al. (2019) (F, G; *RPGRIP1L* mutation), Kheradmand Kia et al. (2012) (H, I; *RTTN* mutation), Putoux et al. (2011) (J, K; *KIF7* mutation), and Juric-Sekhar et al. (2012) (L, M; *OFD1* mutation). These mutations directly or indirectly disrupt primary cilia signaling and maintenance.

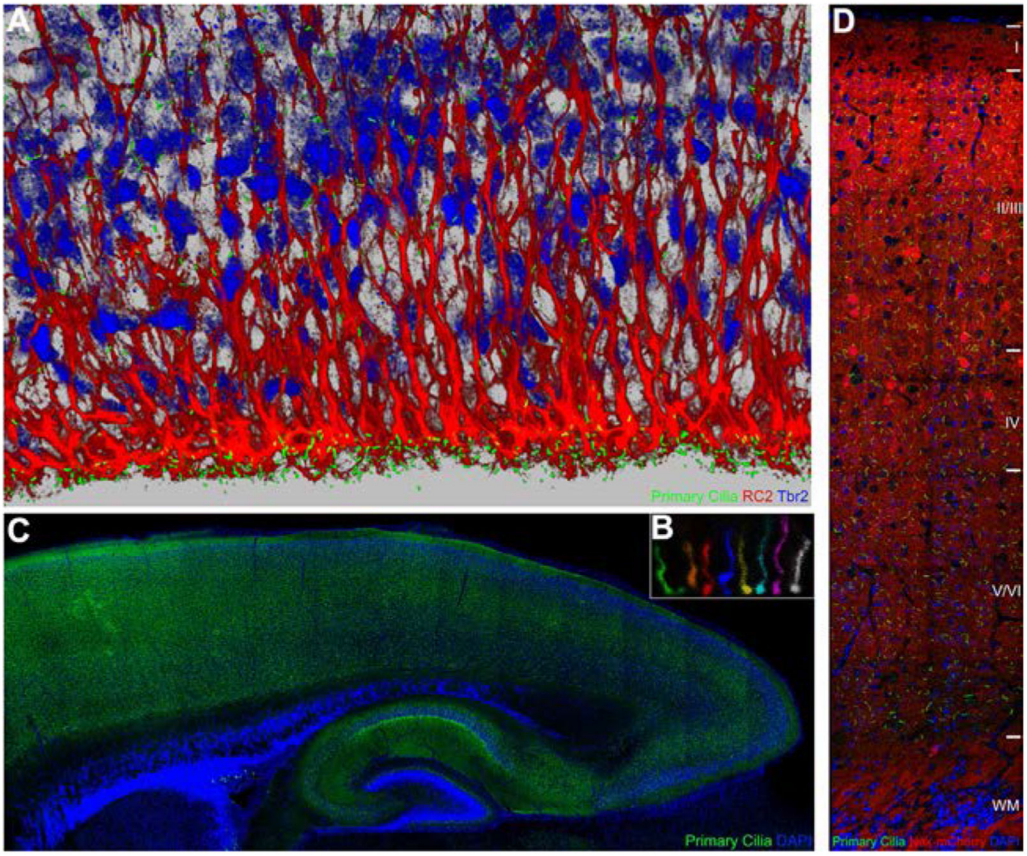

Fig. 2.

Primary cilia in the embryonic and postnatal cerebral cortex. Primary cilia (green) in the ventricular zone of the developing mouse cerebral cortex (E16) were labeled with hGFAP-Cre induced Sstr3-GFP (A). Radial glia and intermediate progenitors were co-labeled with RC2 (red) and anti-Tbr2 (blue) antibodies, respectively. (B) Live imaging of a primary cilium in the embryonic cerebral wall (E16), over 5.5 h, indicates its dynamic nature. Images at different time points were pseudocolored to illustrate the changing shape, length, and orientation. (C) Projection neuronal primary cilia in postnatal brains (P7) were labeled with Nex-Cre induced Sstr3-GFP (B). Neurons across cortical layers display primary cilia of varying shapes and orientation (C).

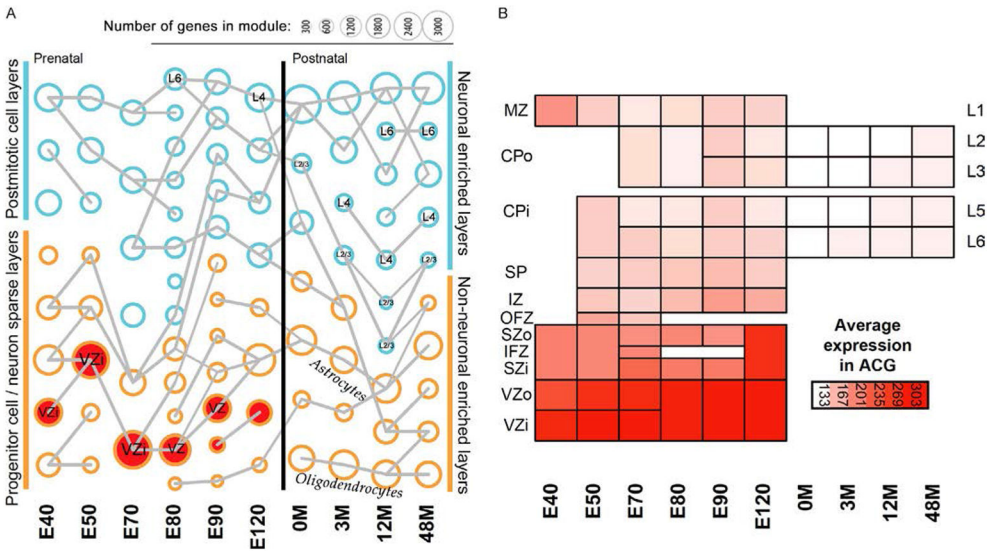

Fig. 3.

Ciliopathy gene expression profile in the developing primate brain. (A) Gene expression levels of distinct populations of cells in individual cortical layers were profiled in rhesus monkey brain at 10 different pre and postnatal ages (E40, E50, E70, E80, E90, E120, 0M, 3M, 12M, and 48M; Bakken et al., 2016). Ciliopathy associated genes (confirmed and candidate) were significantly enriched among genes co-expressed in the developing cortex, primarily in the proliferative niche and new born neurons. Circle size indicates how many genes are in the module. Modules significantly enriched for risk genes associated with ciliopathies are in red ($P < 0.1$). Modules from adjacent ages with the most highly significant gene overlap are connected by gray lines. Though the number of ciliopathy genes overlapping with the other modules did not reach statistical significance, different ciliopathy genes are expressed in these modules (see Table 1). (B) Average expression pattern of cilia associated genes found in at least two enriched modules. Heat maps are organized by specific cortical layer and age as described in Bakken et al. (2016). MZ, marginal zone; CPo/CPi, outer/inner cortical plate; SP, subplate; IZ, intermediate zone; SZ, subventricular zone; VZo/VZi, outer/inner ventricular zone; L2-6, cortical neuronal layers 2–6.

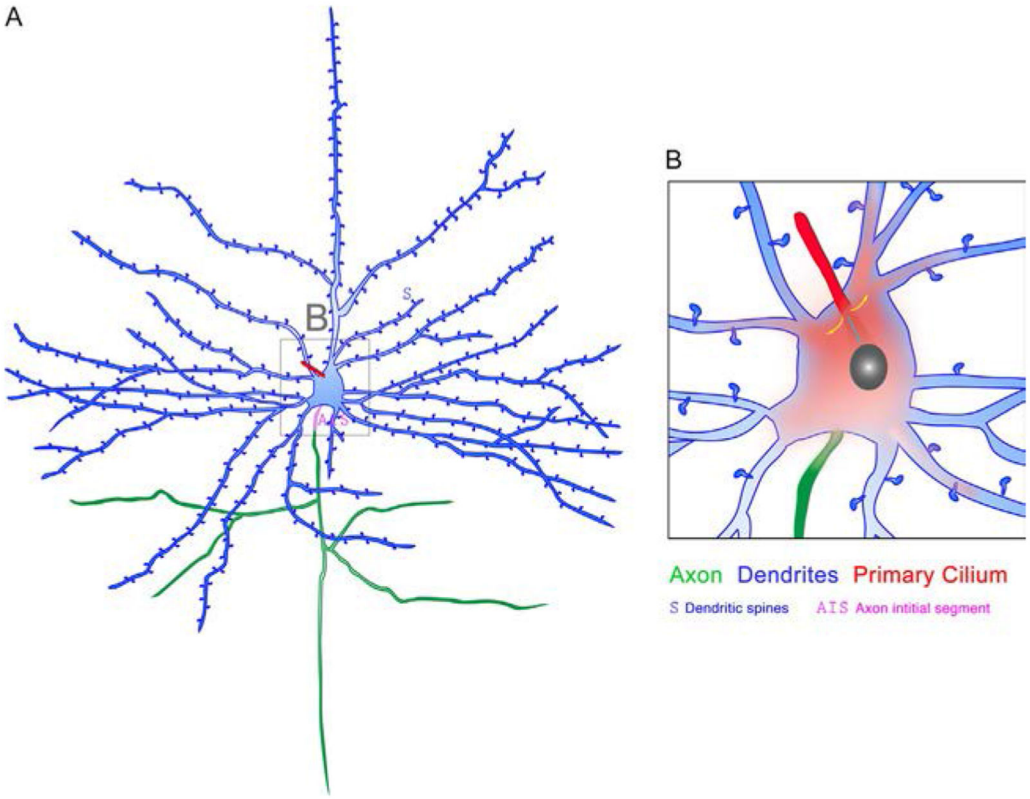

Fig. 4.

Understanding the functional importance of primary cilia in neurons. Interrogating the selective effect of signaling emanating from primary cilia on axons and dendrites and defining how signaling spreads from the primary cilium to distal domains of neurons (red gradient) and to the nucleus (cyan arrow) to influence neuronal activity and behavior are challenges yet to be met. A similar dearth of knowledge exists for the importance of primary cilia signaling during glial cell development and behavior.

Table 1

Ciliopathy and cilia-associated genes in gene expression modules of different cell types in the developing primate brain (related to Fig. 3).

a

Cortical gene expression modules	Total number of genes in module	% Ciliopathy genes in module	List of ciliopathy (confirmed and candidate) genes in module
BAKKEN2016_WGCNA_E40_M00	2484	2.254428341	ADCY6,AIPL1,AKAP9,ARF4,ARL2BP,ARL6,B9D1,BBS4,BBS7,CCNO, CEP104,CEP19,CP110,DCDC2,DNAH5,DNAI1,DNAL4,DNALI1,EFCAB7, HNF1B,HYDIN,INVS,IQCE,KIF24,LCA5,LRAT,LRRC49,LRRC6,MLF1, MST1,NEK1,NIN,NPHP3,NPHP4,OFD1,PACRG,PIH1D3,PKD1, POMGNT1,PTCH1,PTK7,PTPDC1,RAB3IP,RFX3,ROPN1L,RPE65, RSPH1,SPAG1,SPAG6,SSX2IP,TEKT1,TMEM107,TMEM17,TPRA1,TUBE1, TUBGCP6
BAKKEN2016_WGCNA_E40_M01	1621	1.480567551	CCDC28B,CEP170,CRB3,CTTN,DCTN1,KIF17,KIF3A,KIF3B,KIF3C, KIF5C,KIFAP3,MARK4,MCHR1,MXI1,NME7,OCRL,PRKACB,RAB11A, SDCCAG8,7-SEP,SNX10,TTBK2,USP9X,WDR60
BAKKEN2016_WGCNA_E40_M02	803	2.615193026	CCDC151,CETN2,GALNT11,GNAS,GSK3A,IFT140,IFT52,INPP5E, KATNB1,KIF2A,MAPRE1,ODF2,PDE6D,PEBP1,PPP2R1A,PRKAR2B, RAB11B,RAB11FIP3,TUBB,TUBB2B
BAKKEN2016_WGCNA_E40_M03	1271	1.41620771	ANO2,ARMC4,CNGB1,CYS1,DNAH6,GLI1,MAK,MORN3,PKHD1, PRKACA,RAB17,RDH12,RSG1,RSPH4A,SUFU,TTC21A,TTC25, ZMYND10
BAKKEN2016_WGCNA_E40_M04	596	1.006711409	KIF27,KIF7,MDM1,RSPH3,STK38L,TAPT1
BAKKEN2016_WGCNA_E40_M05	1107	1.445347787	C2CD3,CCDC22,CEP250,CEP89,CNTROB,GPR161,HTT,IFT122,MCRS1, MKKS,NUBP1,NUBP2,PAFAH1B1,RABL5,SSNA1,TCTN3,TULP3
BAKKEN2016_WGCNA_E40_M06	1863	1.986044015	AURKA,B9D2,BBS2,BBS9,CEP192,CEP72,CEP76,CEP97,CLUAP1,DNAL1, EVC2,FAM161A,FGFR1OP,GNAI2,GNAI3,HEATR2,IFT88,INPP5B, KIAA0586,MKS1,NEK9,ORC1,PLK1,POC1A,RAB23,RAB28,RILPL2, RTTN,SAV1,2- SEP,SMO,SYNE2, TCTN1,TMEM138,TMEM231,TTC17,WRAP73
BAKKEN2016_WGCNA_E40_M07	1603	4.304429195	AHI1,ALMS1,ANKS6,ARL13B,ASAP1,ATXN10,BBS10,BBS5,BUB1B, CC2D2A,CCDC14,CENPF,CENPJ,CEP120,CEP128,CEP135,CEP152, CEP290,CEP350,CEP63,CEP78,CETN3,CRB1,CROCC,CSPP1,DZIP1, EFHC1,FAM58A,FOXJ1,GLI3,HSPB11,IFT172,IFT57,IFT74,IFT80,IQCB1, IQUB,KCNJ13,KIF14,LZTFL1,MNS1,NEK2,PARD3,PCM1,PHF17,PIK3R4, PKD2,PLK4,POC1B,RFX2,RPGRIP1L,SASS6,SPA17,SPAG16,SPATA7, SPICE1,STIL,STK3,STK39,TEX9,TMEM216,TMEM67,TRIM32,TRIP11, TTC30A,TTC30B,TTC8,WDR19,WDR35
BAKKEN2016_WGCNA_E40_M08	1093	0.640439158	MAL,MERTK,RP2,TBX3,TUBA4A,WNK1,ZIC2

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Cortical gene expression modules	Total number of genes in module	% Ciliopathy genes in module	List of ciliopathy (confirmed and candidate) genes in module
BAKKEN2016_WGCNA_E50_M00	3475	1.928057554	AHI1,AIPL1,ANKS6,ANO2,ARF4,ARL2BP,ARL6,ARMC4,BBS10,BBS7, CCNO,CEP290,CEP72,CEP97,CETN2,CNGB1,CP110,CSPP1,CYS1, DCDC2,DNAH5,DNAH6,GPR161,HNF1B,HYDIN,IFT140,INPP5E,INVS, IQCE,KCNJ13,KIF17,KIF27,LCA5,LRAT,LRRC6,MAK,MCHR1,MKKS, MLF1,MST1,NEK1,NPHP3,PKD1,PKHD1,PRKACA,PTPDC1,RAB17, RFX3,RPE65,RSG1,RSPH1,RSPH3,RSPH4A,SPAG6,SPATA7,SSX2IP, SUFU,TCTN3,TEKT1,TMEM67,TRIM32,TTC17,TTC21A,TTC30A, TUBE1,WDR35,ZMYND10
BAKKEN2016_WGCNA_E50_M01	1295	1.467181467	CEP19,EFCAB7,GALNT11,KIF2A,LRRC49,MORN3,NIN,NME7,PACRG, PRKACB,PRKAR2B,RAB3IP,RDH12,ROPN1L,SNX10,TAPT1,TMEM17, TTBK2,USP9X
BAKKEN2016_WGCNA_E50_M02	1304	1.303680982	AKAP9,ATXN10,CCDC28B,CEP104,CEP170,CRB3,CTTN,HSPB11,KIF3A, KIF3B,KIF3C,KIF5C,KIFAP3,MXI1,OCRL,RAB11A,SDCCAG8
BAKKEN2016_WGCNA_E50_M03	799	1.627033792	CCDC151,DCTN1,GSK3A,KATNB1,MAPRE1,MARK4,PDE6D,PEBP1, POMGNT1,PPP2R1A,RAB11B,TUBB,TUBB2B
BAKKEN2016_WGCNA_E50_M04	518	1.158301158	DNAL4,GNAS,IFT52,NUBP2,TUBGCP6,WRAP73
BAKKEN2016_WGCNA_E50_M05	1079	1.668211307	B9D2,C2CD3,CCDC22,CEP250,CEP89,CNTROB,FAM58A,GNAI2,HTT, IFT122,INPP5B,KIF7,MCRS1,NUBP1,PAFAH1B1,RAB11FIP3,RABL5, SSNA1,TUBA4A
BAKKEN2016_WGCNA_E50_M06	2916	3.429355281	ADCY6,ALMS1,ARL13B,ASAP1,AURKA,B9D1,BBS2,BBS4,BBS5,BBS9, BUB1B,CC2D2A,CCDC14,CENPF,CENPJ,CEP120,CEP128,CEP135, CEP152,CEP192,CEP350,CEP63,CEP76,CEP78,CETN3,CLUAP1,CRB1, CROCC,DNAI1,DNAL1,DNALI1,DZIP1,EFHC1,EVC2,FAM161A, FGFR1OP,FOXJ1,GLI1,GLI3,GNAI3,HEATR2,IFT172,IFT57,IFT74,IFT80, IFT88,IQCB1,iQuB,KIAA0586,KIF14,KIF24,LZTFL1,MDM1,MKS1,MNS1, NEK2,NEK9,NPHP4,ODF2,ORC1,PARD3,PCM1,PHF17,PIH1D3,PIK3R4, PKD2,PLK1,PLK4,POC1A,POC1B,PTCH1,PTK7,RAB23,RAB28,RFX2, RILPL2,RP2,RPGRIP1L,RTTN,SASS6,SAV1,2-SEP, SMO,SPA17,SPAG1,SPAG16,SPICE1,STIL,STK3,STK38L,STK39,SYNE2, TCTN1,TEX9,TMEM107,TMEM138,TMEM216,TMEM231,TPRA1, TRIP11,TTC30B,TTC8,TULP3,WDR19,ZIC2
BAKKEN2016_WGCNA_E50_M07	578	0.346020761	MAL,TBX3
BAKKEN2016_WGCNA_E50_M08	477	1.257861635	MERTK,OFD1,7-SEP,TTC25,WDR60,WNK1
BAKKEN2016_WGCNA_E70_M00	3085	1.458670989	ADCY6,ANKS6,ARL2BP,ARMC4,ASAP1,CEP72,CEP78,CEP89,CLUAP1, CP110,CRB3,DCDC2,DNAH5,DNAH6,EFHC1,HNF1B,HYDIN,INPP5E, INVS,KIF27,LRAT,MAL,MCHR1,MKKS,MLF1,MORN3,MST1,NEK1, NPHP3,PKD1,POMGNT1,PTK7,PTPDC1,ROPN1L,RPE65,SAV1,SPA17, SPAG1,TBX3,TRIM32,TTC17,TTC21A,TTC30B,TUBGCP6,WNK1
BAKKEN2016_WGCNA_E70_M01	1240	1.048387097	CEP19,GALNT11,IQCE,KIF3A,LRRC49,MAK,NIN,NME7,PRKACB, RAB3IP,RDH12,SNX10,TMEM17

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Cortical gene expression modules	Total number of genes in module	% Ciliopathy genes in module	List of ciliopathy (confirmed and candidate) genes in module
BAKKEN2016_WGCNA_E70_M02	1405	0.996441281	CCDC28B,DCTN1,GSK3A,KIF2A,KIF3B,KIF3C,KIF5C,KIFAP3,OCRL, PEBP1,PPP2R1A,PRKAR2B,RAB11A,SDCCAG8
BAKKEN2016_WGCNA_E70_M03	1164	2.319587629	AKAP9,ARF4,ARL6,ATXN10,BBS10,BBS7,CEP104,CEP120,CEP170, CEP350,CSPP1,EFCAB7,FAM58A,HSPB11,IFT57,IFT80,MXI1,OFD1,RFX3, SPATA7,SSX2IP,TAPT1,TTBK2,TUBE1,USP9X,WDR35,WDR60
BAKKEN2016_WGCNA_E70_M04	1116	1.702508961	AIPL1,ANO2,CCNO,CEP290,CEP97,CNGB1,CYS1,KIF17,LRRC6,MARK4, PKHD1,PRKACA,RAB17,RSG1,RSPH4A,SPAG6,SUFU,TTC25,ZMYND10
BAKKEN2016_WGCNA_E70_M05	1315	2.053231939	B9D2,C2CD3,CCDC22,CEP250,CETN2,CNTROB,CTTN,DNAL4,GNAS, GPR161,HTT,IFT122,IFT140,IFT52,KATNB1,KIF7,MAPRE1,MCRS1, NPHP4,NUBP1,NUBP2,PDE6D,RAB11B,RSPH3,TUBB,TUBB2B,WRAP73
BAKKEN2016_WGCNA_E70_M06	3116	3.498074454	AHI1,ALMS1,ARL13B,AURKA,B9D1,BBS2,BBS4,BBS5,BBS9,BUB1B, CC2D2A,CCDC14,CCDC151,CENPF,CENPJ,CEP128,CEP135,CEP152, CEP192,CEP63,CEP76,CETN3,CRB1,CROCC,DNAI1,DNAL1,DNALI1, DZIP1,EVC2,FAM161A,FGFR1OP,FOXJ1,GLI1,GLI3,GNAI2,GNAI3, HEATR2,IFT172,IFT74,IFT88,INPP5B,IQCB1,IQUB,KCNJ13,KIAA0586, KIF14,KIF24,LCA5,LZTFL1,MDM1,MERTK,MKS1,MNS1,NEK2,NEK9, ODF2,ORC1,PACRG,PAFAH1B1,PARD3,PCM1,PHF17,PIH1D3,PIK3R4, PKD2,PLK1,PLK4,POC1A,POC1B,PTCH1,RAB11FIP3,RAB23,RAB28, RABL5,RFX2,RILPL2,RP2,RPGRIP1L,RSPH1,RTTN,SASS6,2-SEP,7-SEP, SMO,SPAG16,SPICE1,SSNA1,STIL,STK3, STK38L,STK39,SYNE2,TCTN1,TCTN3,TEKT1,TEX9,TMEM107, TMEM138,TMEM216,TMEM231,TMEM67,TPRA1,TRIP11,TTC30A,TTC8, TUBA4A,TULP3,WDR19,ZIC2
BAKKEN2016_WGCNA_E80_M00	3065	1.924959217	ADCY6,AIPL1,ANKS6,ANO2,ARL2BP,ARMC4,ASAP1,BBS9,CCDC151, CCNO,CEP135,CEP290,CEP350,CEP72,CEP78,CEP97,CNGB1,CP110, CRB3,CYS1,DNAH6,DNAL1,EFHC1,GLI1,HNF1B,HYDIN,INVS,KIF27, LRAT,LRRC6,MAL,MCHR1,MORN3,MST1,NIN,NPHP4,ODF2,PKD1, PKHD1,PRKACA,PTPDC1,RAB17,RFX3,RPE65,RSG1,RSPH3,RSPH4A, SAV1,SPAG1,SPAG6,SUFU,TCTN1,TCTN3,TMEM67,TPRA1,TTBK2, TTC21A,TTC25,WDR60
BAKKEN2016_WGCNA_E80_M01	936	0.854700855	KIFAP3,NME7,RAB3IP,RDH12,ROPN1L,SNX10,TAPT1,TMEM17
BAKKEN2016_WGCNA_E80_M02	434	1.152073733	AHI1,KIF17,MAK,OCRL,POMGNT1
BAKKEN2016_WGCNA_E80_M03	691	2.604920405	AKAP9,ARL6,ATXN10,CEP104,CEP170,CEP19,GALNT11,IFT57,KIF2A, KIF3A,LRRC49,MKKS,PRKACB,PRKAR2B,SPA17,SSX2IP,TRIM32, USP9X
BAKKEN2016_WGCNA_E80_M04	534	0.561797753	KIF3B,KIF3C,KIF5C
BAKKEN2016_WGCNA_E80_M05	364	0.549450549	CCDC28B,PEBP1
BAKKEN2016_WGCNA_E80_M06	834	2.757793765	ARF4,BBS10,BBS5,BBS7,CEP120,CEP76,CETN2,CSPP1,EFCAB7,FAM161A, HSPB11,IFT80,MDM1,MLF1,PHF17,PIK3R4,RAB11A,RAB23,RAB28, RPGRIP1L,SPATA7,TTC30A,TUBE1

a

Cortical gene expression modules	Total number of genes in module	% Ciliopathy genes in module	List of ciliopathy (confirmed and candidate) genes in module
BAKKEN2016_WGCNA_E80_M07	373	0.536193029	IQCE,TUBGCP6
BAKKEN2016_WGCNA_E80_M08	660	2.272727273	C2CD3,CEP250,CTTN,DCTN1,DNAL4,GSK3A,HTT,IFT122,IFT140, INPP5E,KATNB1,MARK4,NUBP2,PPP2R1A,RAB11B
BAKKEN2016_WGCNA_E80_M09	1096	1.551094891	B9D2,CCDC22,CEP89,CNTROB,FAM58A,GNAS,GPR161,IFT52,MAPRE1, MCRS1,NUBP1,PDE6D,SSNA1,TTC17,TUBB,TUBB2B,WRAP73
BAKKEN2016_WGCNA_E80_M10	835	2.395209581	ARL13B,CCDC14,CEP192,CETN3,GNAI3,HEATR2,IFT88,IQCB1,LCA5, NEK1,POC1B,RP2,RTTN,SASS6,7-SEP,STK38L, STK39,TRIP11,TTC8,WDR35
BAKKEN2016_WGCNA_E80_M11	371	0.808625337	MERTK,MXI1,RSPH1
BAKKEN2016_WGCNA_E80_M12	1952	3.790983607	ALMS1,AURKA,B9D1,BBS2,BBS4,BUB1B,CC2D2A,CENPF,CENPJ, CEP128,CEP152,CEP63,CLUAP1,CRB1,CROCC,DCDC2,DNAH5,DNAI1, DNALI1,DZIP1,EVC2,FGFR1OP,FOXJ1,GLI3,GNAI2,IFT172,IFT74, INPP5B,IQUB,KCNJ13,KIAA0586,KIF14,KIF24,KIF7,LZTFL1,MKS1,MNS1, NEK2,NEK9,NPHP3,ORC1,PACRG,PAFAH1B1,PARD3,PCM1,PIH1D3, PKD2,PLK1,PLK4,POC1A,PTCH1,PTK7,RAB11FIP3,RABL5,RFX2, RILPL2,2-SEP,SMO,SPAG16,SPICE1,STIL,STK3,SYNE2,TEKT1,TEX9, TMEM107,TMEM138,TMEM216,TMEM231,TTC30B,TUBA4A,TULP3, WDR19,ZIC2,ZMYND10
BAKKEN2016_WGCNA_E80_M13	296	1.351351351	OFD1,SDCCAG8,TBX3,WNK1
BAKKEN2016_WGCNA_E90_M00	3082	1.26541207	ADCY6,AIPL1,ANKS6,ANO2,ARL2BP,CEP192,CEP250,CEP89,CEP97, CNGB1,CP110,CRB3,CYS1,FAM161A,HNF1B,INPP5E,INVS,IQCE,KIF7, LRAT,MCHR1,MST1,NIN,NPHP4,OFD1,PKD1,PKHD1,PRKACA,RAB17, RFX3,RPE65,RSG1,SAV1,SDCCAG8,SUFU,TRIP11,TUBA4A,TUBGCP6
BAKKEN2016_WGCNA_E90_M01	1285	1.322957198	AKAP9,CEP170,CEP19,CEP72,GALNT11,KIF2A,KIF3A,KIFAP3,LRRC49, NME7,PRKACB,PRKAR2B,RAB3IP,SNX10,SSX2IP,TAPT1,TMEM17, USP9X
BAKKEN2016_WGCNA_E90_M02	941	0.743889479	KIF17,KIF3B,KIF3C,KIF5C,MKKS,OCRL,RDH12
BAKKEN2016_WGCNA_E90_M03	852	1.76056338	C2CD3,CCDC28B,DCTN1,GPR161,GSK3A,HTT,KATNB1,MARK4, PDE6D,PEBP1,PPP2R1A,RAB11A,TTC17,TUBB,TUBB2B
BAKKEN2016_WGCNA_E90_M04	923	1.19176598	CNTROB,CTTN,DNAL4,GNAS,HSPB11,IFT52,MCRS1,NUBP1,NUBP2, ODF2,RAB11B
BAKKEN2016_WGCNA_E90_M05	1043	2.396931927	ARF4,ARL6,ASAP1,ATXN10,BBS10,BBS5,BBS7,CEP104,CEP120,CEP76, CSPP1,EFCAB7,FAM58A,IFT57,IFT80,MDM1,MLF1,PIK3R4,RAB23, RAB28,SPATA7,STK39,TRIM32,TUBE1,WRAP73
BAKKEN2016_WGCNA_E90_M06	587	1.022146508	CEP290,CEP350,MXI1,PHF17,TTBK2,WDR60
BAKKEN2016_WGCNA_E90_M07	336	0.595238095	MAL,TBX3
BAKKEN2016_WGCNA_E90_M08	363	0.275482094	MERTK

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Cortical gene expression modules	Total number of genes in module	% Ciliopathy genes in module	List of ciliopathy (confirmed and candidate) genes in module
BAKKEN2016_WGCNA_E90_M09	712	2.106741573	B9D2,CCDC22,CETN2,EVC2,GNAI2,IFT140,KIAA0586,MAPRE1, PAFAH1B1,POMGNT1,RAB11FIP3,RABL5,SSNA1,TCTN1,TMEM138
BAKKEN2016_WGCNA_E90_M10	1615	3.343653251	ARL13B,AURKA,BBS2,BUB1B,CC2D2A,CCDC14,CENPF,CENPJ,CEP152, CEP63,CETN3,CRB1,DZIP1,GLI1,GLI3,GNAI3,IFT74,IFT88,INPP5B, IQCB1,KIF14,LCA5,MKS1,MNS1,NEK1,NEK2,NEK9,NPHP3,ORC1, PARD3,PKD2,PLK1,PLK4,POC1A,POC1B,PTCH1,PTK7,PTPDC1,RILPL2, RP2,RTTN,SASS6,2-SEP,7-SEP,SMO,SPICE1,STIL,STK3,STK38L,SYNE2, TEX9,TMEM107,TMEM216,TULP3,ZIC2
BAKKEN2016_WGCNA_E90_M11	454	12.99559471	AHI1,ALMS1,ARMC4,B9D1,BBS4,BBS9,CCDC151,CCNO,CEP128,CEP135, CEP78,CLUAP1,CROCC,DCDC2,DNAH5,DNAH6,DNAI1,DNAL1, DNALI1,EFHC1,FGFR1OP,FOXJ1,HEATR2,HYDIN,IFT122,IFT172,IQUB, KCNJ13,KIF24,KIF27,LRRC6,LZTFL1,MAK,MORN3,PACRG,PCM1, PIH1D3,RFX2,ROPN1L,RPGRIP1L,RSPH1,RSPH3,RSPH4A,SPA17, SPAG1,SPAG16,SPAG6,TCTN3,TEKT1,TMEM231,TMEM67,TPRA1, TTC21A,TTC25,TTC30A,TTC30B,TTC8,WDR19,WDR35,ZMYND10
BAKKEN2016_WGCNA_E90_M12	248	0.403225806	WNK1
BAKKEN2016_WGCNA_E120_M00	3095	1.357027464	ADCY6,AHI1,AIPL1,ANO2,AURKA,C2CD3,CCDC14,CCDC22,CENPJ, CEP104,CEP135,CEP192,CEP350,CEP89,CEP97,CNGB1,CRB3,CTTN, CYS1,FAM161A,FAM58A,GPR161,IFT57,IFT80,KIF17,LRAT,MAPRE1, MCHR1,NIN,ODF2,PAFAH1B1,PKD1,POMGNT1,PRKACA,RAB17, RAB23,RPE65,SASS6,SSNA1,SUFU,SYNE2,TMEM17,TUBGCP6
BAKKEN2016_WGCNA_E120_M01	1673	1.434548715	ARF4,ASAP1,CEP19,CEP72,CEP76,GALNT11,INVS,KIF2A,KIF3A,KIFAP3, LRRC49,MKKS,NME7,PKHD1,PRKACB,PRKAR2B,RAB3IP,RDH12, SNX10,SSX2IP,STK39,TAPT1,TRIM32,USP9X
BAKKEN2016_WGCNA_E120_M02	1182	0.846023689	CCDC28B,IQCE,KIF3B,KIF3C,KIF5C,OCRL,PDE6D,PEBP1,TUBB, TUBB2B
BAKKEN2016_WGCNA_E120_M03	921	1.520086862	CEP250,CNTROB,DCTN1,GNAS,GSK3A,HTT,INPP5E,MARK4,MCRS1, NUBP1,NUBP2,PPP2R1A,RAB11B,WRAP73
BAKKEN2016_WGCNA_E120_M04	1167	1.199657241	AKAP9,ARL6,ATXN10,BBS7,CEP120,CEP170,EFCAB7,PHF17,PIK3R4, RAB11A,RAB28,TTBK2,TTC17,TUBE1
BAKKEN2016_WGCNA_E120_M05	594	1.346801347	DZIP1,KIF14,MAL,ORC1,PLK1,7-SEP,TBX3,TUBA4A
BAKKEN2016_WGCNA_E120_M06	2158	1.343836886	BUB1B,CENPF,CEP63,GLI1,GLI3,GNAI2,GNAI3,KIF7,MERTK,MXI1, NEK9,NPHP3,PACRG,PARD3,PKD2,POC1A,POC1B,PTCH1,PTK7, RAB11FIP3,RILPL2,RP2,2-SEP,SMO, STK3,STK38L,TMEM216,TPRA1,ZIC2

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Cortical gene expression modules	Total number of genes in module	% Ciliopathy genes in module	List of ciliopathy (confirmed and candidate) genes in module
BAKKEN2016_WGCNA_E120_M07	1253	8.858739026	ALMS1,ANKS6,ARL13B,ARL2BP,ARMC4,B9D1,B9D2,BBS10,BBS2,BBS4, BBS5,BBS9,CC2D2A,CCDC151,CCNO,CEP128,CEP152,CEP290,CEP78, CETN2,CETN3,CLUAP1,CP110,CRB1,CROCC,CSPP1,DCDC2,DNAH5, DNAH6,DNAI1,DNAL1,DNAL4,DNALI1,EFHC1,EVC2,FGFR1OP,FOXJ1, HEATR2,HNF1B,HSPB11,HYDIN,IFT122,IFT140,IFT172,IFT52,IFT74, IFT88,INPP5B,IQCB1,IQUB,KATNB1,KCNJ13,KIAA0586,KIF24,KIF27, LCA5,LRRC6,LZTFL1,MAK,MDM1,MKS1,MLF1,MNS1,MORN3,MST1, NEK1,NEK2,NPHP4,OFD1,PCM1,PIH1D3,PLK4,PTPDC1,RABL5,RFX2, RFX3,ROPN1L,RPGRIP1L,RSG1,RSPH1,RSPH3,RSPH4A,RTTN,SAV1, SDCCAG8,SPA17,SPAG1,SPAG16,SPAG6,SPATA7,SPICE1,STIL,TCTN1, TCTN3,TEKT1,TEX9,TMEM107,TMEM138,TMEM231,TMEM67,TRIP11, TTC21A,TTC25,TTC30A,TTC30B,TTC8,TULP3,WDR19,WDR35, WDR60,ZMYND10
BAKKEN2016_WGCNA_E120_M08	398	0.251256281	WNK1
BAKKEN2016_WGCNA_0M_M00	2960	1.959459459	ADCY6,AIPL1,ALMS1,ANKS6,ANO2,ASAP1,B9D1,BBS4,CCDC151,CCNO, CENPF,CENPJ,CEP128,CEP135,CEP250,CEP350,CEP97,CNGB1,CP110, CTTN,DNAH6,FGFR1OP,HSPB11,IFT172,INPP5E,IQUB,KCNJ13,KIF24, LRAT,LRRC6,MAK,MCHR1,MNS1,MORN3,ORC1,PAFAH1B1,PIH1D3, PKD1,PLK4,POC1A,PRKACA,RAB11A,RAB11B,RAB3IP,RILPL2,RSPH4A, SAV1,SDCCAG8,SPAG1,SPAG6,SUFU,TMEM107,TMEM138,TMEM67, TTC17,USP9X,WDR60,ZMYND10
BAKKEN2016_WGCNA_0M_M01	3173	2.111566341	AHI1,ATXN10,AURKA,B9D2,C2CD3,CCDC22,CCDC28B,CEP19,CEP72, CEP76,DCTN1,DNAH5,DNAL4,FAM58A,GALNT11,GPR161,GSK3A,HTT, IFT122,IFT57,INVS,KATNB1,KIF17,KIF2A,KIF3A,KIF3B,KIF3C,KIF5C, KIFAP3,LRRC49,MARK4,MCRS1,MKKS,NEK2,NME7,NPHP4,NUBP1, NUBP2,OCRL,PDE6D,PEBP1,PHF17,PKHD1,PPP2R1A,PRKAR2B,RAB17, RABL5,RDH12,ROPN1L,RSPH1,RSPH3,SNX10,SPA17,SSX2IP,STIL, SYNE2,TCTN1,TCTN3,TEKT1,TMEM17,TRIM32,TTBK2,TUBA4A, TUBB,TUBB2B,TUBGCP6,WRAP73
BAKKEN2016_WGCNA_0M_M02	714	1.120448179	BBS9,CC2D2A,CYS1,DCDC2,DNAL1,GNAS,HNF1B,IQCE
BAKKEN2016_WGCNA_0M_M03	1079	1.853568119	AKAP9,ARF4,ARL6,BBS5,CEP192,CEP78,CETN2,CLUAP1,EFCAB7, EFHC1,FAM161A,IFT52,IFT80,LZTFL1,MLF1,PIK3R4,RAB28,RFX3, RPGRIP1L,SPATA7
BAKKEN2016_WGCNA_0M_M04	783	2.426564496	ARL2BP,BBS10,BBS7,BUB1B,CEP120,CEP170,CEP63,CSPP1,LCA5,MDM1, NIN,PRKACB,7-SEP,SPICE1,TAPT1,TTC30A,TTC8,TUBE1,WDR19
BAKKEN2016_WGCNA_0M_M05	1853	1.726929304	BBS2,CNTROB,CRB3,CROCC,DNAI1,EVC2,GLI3,GNAI2,GNAI3,IFT140, KIAA0586,MST1,NEK1,NEK9,NPHP3,PARD3,PKD2,POC1B,PTCH1,PTK7, RAB11FIP3,RFX2,RPE65,2-SEP,SMO,SPAG16,STK3,STK38L,TMEM216, TTC21A,TULP3,ZIC2
BAKKEN2016_WGCNA_0M_M06	526	1.330798479	DZIP1,GLI1,KIF7,MERTK,MXI1,ODF2,TBX3

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Cortical gene expression modules	Total number of genes in module	% Ciliopathy genes in module	List of ciliopathy (confirmed and candidate) genes in module
BAKKEN2016_WGCNA_0M_M07	1353	3.17812269	ARL13B,ARMC4,CCDC14,CEP104,CEP152,CEP290,CEP89,CETN3,CRB1, DNALI1,FOXJ1,HEATR2,HYDIN,IFT74,IFT88,INPP5B,IQCB1,KIF14, KIF27,MAL,MAPRE1,MKS1,OFD1,PACRG,PCM1,PLK1,POMGNT1, PTPDC1,RAB23,RP2,RSG1,RTTN,SASS6,SSNA1,STK39,TEX9,TMEM231, TPRA1,TRIP11,TTC25,TTC30B,WDR35,WNK1
BAKKEN2016_WGCNA_3M_M00	2279	2.237823607	ADCY6,AIPL1,ALMS1,ANKS6,ANO2,ARMC4,B9D1,BBS4,CENPJ,CEP128, CEP135,CEP350,CEP78,CEP97,CLUAP1,CNGB1,CROCC,CSPP1,EFHC1, FOXJ1,GLI1,HNF1B,HYDIN,IFT74,INPP5B,KCNJ13,KIF14,KIF24,KIF27, KIF7,LRAT,LRRC6,MAK,MORN3,MST1,NIN,ORC1,PIH1D3,PKHD1, PLK1,PRKACA,PTK7,RAB11A,RAB11B,RAB3IP,SAV1,SDCCAG8,SUFU, TEX9,TTC21A,WDR19
BAKKEN2016_WGCNA_3M_M01	2318	1.98446937	AHI1,ARL6,ASAP1,ATXN10,C2CD3,CCNO,CYS1,DNAH6,DNAL1, DNAL4,GNAS,GSK3A,HTT,IFT57,INPP5E,INVS,IQCE,KATNB1,KIF3A, KIF3B,KIF3C,KIF5C,KIFAP3,LRRC49,MARK4,NME7,NPHP4,OCRL, PEBP1,POC1A,RAB17,RSPH1,RSPH3,SNX10,SSX2IP,STIL,TCTN3,TEKT1, TMEM17,TMEM67,TRIM32,TTBK2,TTC17,TUBA4A,TUBB,USP9X
BAKKEN2016_WGCNA_3M_M02	1448	1.726519337	B9D2,BBS9,CCDC151,CCDC22,CEP76,CETN2,DCTN1,FAM58A, FGFR1OP,GALNT11,IFT172,IFT80,LZTFL1,MKKS,NUBP1,NUBP2,PDE6D, ROPN1L,SPA17,SPAG1,SPAG6,SPATA7,TUBGCP6,WDR60,WRAP73
BAKKEN2016_WGCNA_3M_M03	584	2.739726027	AURKA,BBS7,BUB1B,CCDC28B,CENPF,CTTN,GPR161,IFT122,MCRS1, PHF17,PKD1,PPP2R1A,RDH12,SYNE2,TTC25
BAKKEN2016_WGCNA_3M_M04	678	2.212389381	CC2D2A,CEP72,DCDC2,DNAH5,HSPB11,KIF17,MCHR1,MLF1,NEK2, PRKAR2B,PTCH1,RFX3,RSPH4A,TUBB2B,ZMYND10
BAKKEN2016_WGCNA_3M_M05	1227	1.711491443	AKAP9,ARF4,ARL2BP,BBS10,BBS5,CEP120,CEP19,CEP192,EFCAB7, FAM161A,IFT52,KIF2A,MDM1,PAFAH1B1,PIK3R4,PLK4,RAB28,RABL5, RPGRIP1L,TTC8,WDR35
BAKKEN2016_WGCNA_3M_M06	1489	1.813297515	BBS2,CEP250,CRB1,DNAI1,DNALI1,EVC2,GLI3,GNAI2,GNAI3,KIAA0586, MXI1,NEK1,NEK9,NPHP3,PACRG,PARD3,PCM1,RAB11FIP3,RFX2, RSG1,2-SEP,SMO,STK38L,TMEM107,TMEM216,TULP3,ZIC2
BAKKEN2016_WGCNA_3M_M07	604	1.655629139	CNTROB,DZIP1,IFT140,IQUB,MERTK,MKS1,ODF2,RILPL2,TBX3, TPRA1
BAKKEN2016_WGCNA_3M_M08	1814	2.425578831	ARL13B,CCDC14,CEP104,CEP152,CEP170,CEP290,CEP63,CEP89,CETN3, CP110,CRB3,HEATR2,IFT88,IQCB1,LCA5,MAL,MAPRE1,MNS1,OFD1, PKD2,POC1B,POMGNT1,PRKACB,PTPDC1,RAB23,RP2,RPE65,RTTN, SASS6,7-SEP,SPAG16,SPICE1,SSNA1,STK3,STK39,TAPT1,TCTN1, TMEM138,TMEM231,TRIP11,TTC30A,TTC30B,TUBE1,WNK1
BAKKEN2016_WGCNA_12M_M00	2310	1.904761905	AIPL1,ANO2,ARMC4,AURKA,BBS4,BBS9,BUB1B,CENPJ,CEP128,CEP192, CEP350,CEP72,CEP78,CEP97,CLUAP1,CNGB1,DNAH6,GLI1,HNF1B, IFT140,IFT172,KIF14,KIF24,LRRC6,MAK,MKS1,MORN3,NEK1,NIN, ORC1,PIH1D3,PKD1,PKHD1,PLK1,POC1A,PRKACA,RAB11B,RAB3IP, SAV1,SDCCAG8,SSNA1,TCTN1,TMEM138,ZMYND10

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Cortical gene expression modules	Total number of genes in module	% Ciliopathy genes in module	List of ciliopathy (confirmed and candidate) genes in module
BAKKEN2016_WGCNA_12M_M01	2025	1.827160494	AHI1,ANKS6,ASAP1,B9D2,C2CD3,CCDC151,CCDC22,CCNO,CYS1, DCTN1,DNAL4,FAM58A,GALNT11,GNAS,KATNB1,KIF3B,KIF3C,KIF5C, KIF7,KIFAP3,MCRS1,NPHP4,OCRL,PEBP1,PPP2R1A,RAB17,RSPH1, SNX10,SSX2IP,STIL,TCTN3,TRIM32,TTBK2,TTC17,TUBA4A,TUBGCP6, WRAP73
BAKKEN2016_WGCNA_12M_M02	588	2.040816327	CETN2,DNAH5,DNAL1,FGFR1OP,KIF17,MCHR1,PDE6D,PLK4,RABL5, ROPN1L,TEKT1,TUBB
BAKKEN2016_WGCNA_12M_M03	918	2.178649237	AKAP9,ARL6,CEP19,CEP76,EFCAB7,IFT57,INVS,KIF3A,LRRC49,LZTFL1, MKKS,PRKAR2B,RPGRIP1L,RSPH3,SPA17,SPAG6,SPATA7,TMEM17, USP9X,WDR60
BAKKEN2016_WGCNA_12M_M04	615	1.300813008	ADCY6,CCDC28B,DZIP1,GSK3A,HTT,INPP5E,IQCE,MARK4
BAKKEN2016_WGCNA_12M_M05	671	2.682563338	BBS7,CENPF,CTTN,GPR161,IFT122,INPP5B,MDM1,NME7,NUBP1, NUBP2,PHF17,RDH12,RSPH4A,SPAG1,SYNE2,TMEM67,TTC21A,TTC25
BAKKEN2016_WGCNA_12M_M06	289	0.692041522	MERTK,TBX3
BAKKEN2016_WGCNA_12M_M07	431	1.856148492	ATXN10,B9D1,CC2D2A,DCDC2,HSPB11,KCNJ13,NEK2,PTCH1
BAKKEN2016_WGCNA_12M_M08	1773	1.861252115	ALMS1,BBS2,CNTROB,CRB1,CROCC,DNAI1,DNALI1,EVC2,FOXJ1, GLI3,GNAI2,HYDIN,KIAA0586,NPHP3,ODF2,PACRG,PARD3, RAB11FIP3,RFX2,RILPL2,RSG1,2-SEP,SMO,SUFU,TMEM107,TMEM216, TMEM231,TPRA1,TUBB2B,TULP3,ZIC2
BAKKEN2016_WGCNA_12M_M09	1157	2.679343129	ARF4,ARL2BP,BBS10,BBS5,CEP120,CSPP1,EFHC1,FAM161A,IFT52,IFT74, IFT80,IQUB,KIF2A,LCA5,LRAT,MLF1,MNS1,PAFAH1B1,PIK3R4,RAB11A, RAB28,RFX3,RP2,SPICE1,TAPT1,TEX9,TTC30A,TTC8,TUBE1,WDR19, WDR35
BAKKEN2016_WGCNA_12M_M10	1664	2.584134615	ARL13B,CCDC14,CEP104,CEP135,CEP152,CEP170,CEP250,CEP290, CEP63,CEP89,CETN3,CP110,CRB3,GNAI3,HEATR2,IFT88,IQCB1,KIF27, MAL,MAPRE1,MST1,MXI1,NEK9,OFD1,PCM1,PKD2,POC1B,POMGNT1, PRKACB,PTK7,PTPDC1,RAB23,RPE65,RTTN,SASS6,7-SEP,SPAG16, STK3,STK38L,STK39,TRIP11,TTC30B,WNK1
BAKKEN2016_WGCNA_48M_M00	2109	2.038880986	ANO2,ARL2BP,BBS4,BBS7,BBS9,CENPJ,CEP135,CEP192,CEP97,CNGB1, CSPP1,EFCAB7,EFHC1,FGFR1OP,HNF1B,IQUB,KIAA0586,KIF14,KIF24, KIF27,LRAT,MNS1,NEK1,NME7,ORC1,PDE6D,PHF17,PIH1D3,PKHD1, PLK1,PLK4,RAB11A,RAB11B,RAB3IP,RPGRIP1L,SAV1,SDCCAG8,SPAG1, SUFU,TEX9,TMEM138,TMEM67,WDR19
BAKKEN2016_WGCNA_48M_M01	2217	2.390617952	AHI1,AIPL1,AKAP9,ARL6,ASAP1,C2CD3,CCNO,CEP19,CEP76,CYS1, DNAL1,DNAL4,FAM58A,GALNT11,GNAS,GSK3A,HTT,IFT57,INPP5E, INVS,IQCE,KATNB1,KIF3A,KIF3B,KIF3C,KIF5C,KIF7,KIFAP3,LRRC49, LZTFL1,MARK4,MORN3,OCRL,PEBP1,PRKACA,RAB17,ROPN1L, RSPH1,RSPH3,SNX10,SPA17,SPAG6,SPATA7,SSX2IP,STIL,TCTN3, TMEM17,TRIM32,TTBK2,TTC17,TTC25,TUBA4A,USP9X

Curr Top Dev Biol. Author manuscript; available in PMC 2022 January 07.

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Cortical gene expression modules	Total number of genes in module	% Ciliopathy genes in module	List of ciliopathy (confirmed and candidate) genes in module
BAKKEN2016_WGCNA_48M_M02	570	2.280701754	CEP78,CETN2,CLUAP1,DCDC2,DNAH5,DZIP1,IFT52,KIF17,LRRC6, MCHR1,PRKAR2B,RABL5,TEKT1
BAKKEN2016_WGCNA_48M_M03	1382	1.374819103	ADCY6,ANKS6,B9D2,CCDC151,CCDC22,CCDC28B,DCTN1,DNAH6, IFT140,IFT172,INPP5B,MCRS1,NPHP4,PKD1,POC1A,TTC21A,TUBB, TUBGCP6,WRAP73
BAKKEN2016_WGCNA_48M_M04	744	1.747311828	AURKA,CENPF,CTTN,GPR161,IFT122,MDM1,MKKS,NUBP1, NUBP2,PPP2R1A,RDH12,SYNE2,WDR60
BAKKEN2016_WGCNA_48M_M05	433	1.385681293	B9D1,BUB1B,CC2D2A,GLI1,NEK2,ZMYND10
BAKKEN2016_WGCNA_48M_M06	426	2.112676056	ARMC4,BBS2,CROCC,HSPB11,KCNJ13,MERTK,ODF2,PTCH1,TBX3
BAKKEN2016_WGCNA_48M_M07	1630	2.024539877	ALMS1,CEP250,CRB1,DNAI1,DNALI1,EVC2,FOXJ1,GLI3,GNAI2,GNAI3, MAPRE1,MXI1,NIN,NPHP3,PACRG,PARD3,PTK7,RAB11FIP3,RAB23, RFX2,RILPL2,RSG1,2-SEP,SMO,TCTN1,TMEM107,TMEM216,TMEM231, TRIP11,TTC30B,TUBB2B,TULP3,ZIC2
BAKKEN2016_WGCNA_48M_M08	719	1.529902643	ARF4,ATXN10,BBS5,IFT80,MLF1,PIK3R4,RAB28,RFX3,RSPH4A,TUBE1, WDR35
BAKKEN2016_WGCNA_48M_M09	812	3.448275862	ARL13B,BBS10,CCDC14,CEP120,CEP170,CEP290,CEP350,CEP63,CETN3, CP110,FAM161A,HYDIN,IFT74,IFT88,KIF2A,LCA5,MAK,PCM1,POC1B, RP2,RPE65,SASS6,7-SEP,SPICE1,STK38L,TAPT1,TTC30A,TTC8
BAKKEN2016_WGCNA_48M_M10	1399	1.858470336	CEP104,CEP128,CEP152,CEP72,CEP89,CNTROB,CRB3,HEATR2,IQCB1, MAL,MKS1,MST1,NEK9,OFD1,PAFAH1B1,PKD2,POMGNT1,PRKACB, PTPDC1,RTTN,SPAG16,SSNA1,STK3,STK39,TPRA1,WNK1

Modules with significant enrichment of ciliopathy genes are highlighted (adj P values are below)
BAKKEN2016_WGCNA_E40_M07 4.852e-7; BAKKEN2016_WGCNA_E50_M06 7.030e-9; BAKKEN2016_WGCNA_E70_M06 3.500e-7; BAKKEN2016_WGCNA_E80_M12 2.399e-6; BAKKEN2016_WGCNA_E90_M11 3.492e-29; BAKKEN2016_WGCNA_E120_M07 1.004e-41

b

Ciliopathy and cilia associated genes
ADCY3, ADCY6, AHI1, AIPL1, AK7, AKAP9, ALMS1, ANKRD26, ANKS3, ANKS6, ANO2, ARF4, ARL13B, ARL2, ARL2BP, ARL3, ARL6, ARMC4, ASAP1, ATXN10, AURKA, B9D1, B9D2, BBIP1, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, BUB1B, C10ORF107, C11ORF49, C21ORF2, C21ORF59, C2CD3, C2ORF71, C5orf42, C8orf37, CATIP, CBY1, CC2D2A, CCDC103, CCDC112, CCDC114, CCDC13, CCDC14, CCDC151, CCDC18, CCDC22, CCDC28B, CCDC37, CCDC39, CCDC40, CCDC63, CCDC65, CCDC66, CCDC88A, CCNO, CDK5RAP2, CDKL5, CENPF, CENPJ, CEP104, CEP120, CEP128, CEP131, CEP135, CEP152, CEP162, CEP164, CEP170, CEP19, CEP192, CEP250, CEP290, CEP350, CEP41, CEP63, CEP72, CEP76, CEP78, CEP83, CEP89, CEP97, CETN1, CETN2, CETN3, CFAP126, CFAP161, CFAP20, CFAP36, CFAP410, CFAP52, CFAP53, CFAP54, CFAP57, CFAP58, CFAP61, CLUAP1, CNGA1, CNGA2, CNGA4, CNGB1, CNTROB, CP110, CPLANE2, CRB1, CRB3, CROCC, CRX, CSNK1D, CSPP1, CTTN, CYS1, DCDC2, DCTN1, DDX59, DISC1, DNAAF1, DNAAF2, DNAAF3, DNAAF4, DNAAF5, DNAH1, DNAH10, DNAH11, DNAH2, DNAH5, DNAH6, DNAH9, DNAI1, DNAI2, DNAJB13, DNAL1, DNAL4, DNALI1, DPCD, DRC1, DRC3, DVL1, DYNC2H1, DYNC2LI1, DYNLT1, DYX1C1, DZIP1, EFCAB7, EFHC1, EFHC2, EVC, EVC2, EXOC4, FAM161A, FAM58A, FBF1, FGFR1OP, FIGNL1, FLCN, FOPNL, FOXJ1, FTO, FUZ, GALNT11, GAS8, GDI2, GLI1, GLI2, GLI3, GLIS2, GNAI2, GNAI3, GNAS, GPBAR1, GPR161, GSK3A, GUCY2D, HEATR2, HNF1B, HSPB11, HTR6, HTT, HYDIN, HYLS1, ICK, IFT122, IFT139, IFT140, IFT172, IFT20, IFT27, IFT43, IFT46, IFT52, IFT57, IFT74, IFT80, IFT81, IFT88, IMPDH1, INPP5B, INPP5E, INTU, INVS, IQCB1, IQCE, IQCG, IQUB, KATNB1, KCNJ13, KIAA0556, KIAA0586, KIAA0753, KIAA1217, KIF11, KIF14, KIF17, KIF19, KIF24, KIF27, KIF2A, KIF3A, KIF3B, KIF3C, KIF5C, KIF7, KIFAP3, KIZ, LCA5, LRAT, LRRC49, LRRC6, LUZP1, LZTFL1, MAK, MAL, MAPRE1, MARK4, MCHR1, MCIDAS, MCRS1, MDM1, MERTK, MKKS, MKS1, MLF1, MNS1, MOK, MORN3,

a

Cortical gene expression modules	Total number of genes in module	% Ciliopathy genes in module	List of ciliopathy (confirmed and candidate) genes in module
MST1, MXI1, MYB, NEK1, NEK2, NEK4, NEK8, NEK9, NIN, NINL, NME5, NME7, NME8, NMNAT1, NOTO, NPHP1, NPHP2, NPHP3, NPHP4, NPHP5, NPHP7, NPHP9, NUBP1, NUBP2, OCRL, ODF2, OFD1, ORC1, OSR1, PACRG, PAFAH1B1, PARD3, PCARE, PCM1, PCNT, PDE6D, PEBP1, PHF17, PIBF1, PIFO, PIH1D3, PIK3R4, PKD1, PKD2, PKD1L1, PKD2L1, PKHD1, PLK1, PLK4, POC1A, POC1B, POC5, POMGNT1, PPP1R32, PPP2CA, PPP2R1A, PRKACA, PRKACB, PRKAR1A, PRKAR2A, PRKAR2B, PROSER3, PTCH1, PTK7, PTPDC1, RAB11A, RAB11B, RAB11FIP3, RAB17, RAB23, RAB28, RAB29, RAB3IP, RAB8A, RABL5, RD3, RDH12, RFX2, RFX3, RILPL1, RILPL2, ROPN1, ROPN1L, RP1, RP1L1, RP2, RPE65, RPGR, RPGRIP1, RPGRIP1L, RSG1, RSPH1, RSPH14, RSPH3, RSPH4A, RSPH9, RTTN, SASS6, SAV1, SAXO1, SCLT1, SDCCAG8, SEPT2, SEPT7, SLC47A2, SLC4A1, SMO, SNAP25, SNX10, SPA17, SPAG1, SPAG16, SPAG17, SPAG6, SPATA7, SPEF1, SPEF2, SPICE1, SSNA1, SSTR3, SSX2IP, STIL, STK3, STK36, STK38L, STK39, STOML3, STX3, SUFU, SYNE2, TAPT1, TBC1D31, TBC1D32, TBC1D7, TBX3, TCTEX1D2, TCTN1, TCTN2, TCTN3, TEKT1, TEKT2, TEKT3, TEKT4, TEKT5, TEX9, TMEM107, TMEM138, TMEM17, TMEM216, TMEM231, TMEM237, TMEM67, TMEM80, TOPORS, TPRA1, TRAF3IP1, TRIM32, TRIP11, TTBK2, TTC17, TTC21A, TTC21B, TTC25, TTC26, TTC29, TTC30A, TTC30B, TTC8, TTLL3, TTLL5, TTLL6, TTLL9, TUB, TUBA1A, TUBA1C, TUBA4A, TUBB, TUBB2A, TUBB2B, TUBB3, TUBE1, TUBGCP6, TULP1, TULP3, ULK4, UNC119, USP33, USP9X, VHL, WDPCP, WDR19, WDR34, WDR35, WDR60, WDR62, WDR78, WNK1, WNK4, WRAP73, XPNPEP3, ZIC2, ZMYND10, ZNF423.			

Names of the modules from different embryonic and postnatal ages, total number of genes in each module, % of cilia-related genes in the module, and the ciliary genes in each of the modules are listed in table (a). For a listing of all the genes in different modules, see (Bakken et al., 2016). All the cilia related genes used in this analysis are listed in table (b).

Table (b) compiled from Guo, J., Higginbotham, H., Li, J., Nichols, J., Hirt, J., Ghukasyan, V., & Anton, E. S. (2015). Developmental disruptions underlying brain abnormalities in ciliopathies. *Nature Communications, 6(7857)*. doi:10.1038/ncomms8857; Reiter, J. F., & Leroux, M. R. (2017). Genes and molecular pathways underpinning ciliopathies. *Nature Reviews. Molecular Cell Biology, 18(9)*, 533–547. doi:10.1038/nrm.2017.60.