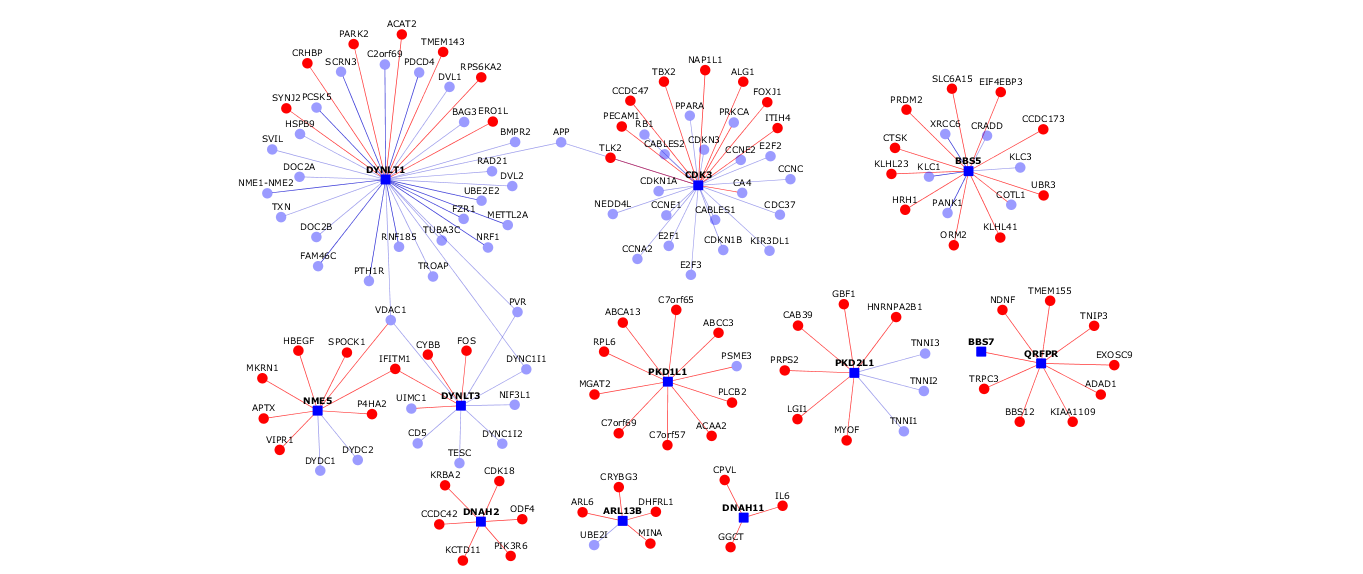
**Cilia interactome with predicted protein-protein interactions reveals connections to Alzheimer’s disease, Aging and other Neuropsychiatric Processes**

Kalyani B. Karunakaran1[[1]](#footnote-1), Srilakshmi Chaparala2,3†, Cecilia W. Lo4 and Madhavi K. Ganapathiraju2,5\*

1Indian Institute of Science, Bangalore, India

2Department of Biomedical Informatics, 3Health Sciences Library System, and 4Department ofDevelopmental Biology, School of Medicine, and 5Intelligent Systems Program, School of Computing and Information, University of Pittsburgh, Pittsburgh, PA, USA

\*To whom correspondence should be addressed: Madhavi K. Ganapathiraju, Department of Biomedical Informatics, University of Pittsburgh, Pittsburgh, PA 15206, USA. madhavi@pitt.edu



**Figure. Some novel PPIs in the Cilia interactome.** Cilia genes are shown as small dark-blue colored nodes and interactor genes are larger round nodes; the interactors are colored in light blue if they are previously known interactors and in red if they are found only through novel PPIs. PPIs are shown as edges, where blue color edges are known PPIs and red color edges are novel predicted PPIs.

## Novel PPIs involved in neuropsychiatric disorders

**LGI1**, associated with temporal lobe epilepsy (seizure disorder), has been predicted as a novel interactor of the ciliary protein **PKD2L1** (figure) (1). **PKD2L1** (*polycystic kidney disease 2-like 1 protein*), which is implicated in epilepsy, controls excitability of neurons and its deficiency leads to loss of primary cilia (2). **LGI1** (*leucine rich glioma inactivated 1*) functions as a negative regulator of excitatory synaptic transmission during post natal development in mice (3). Mice lacking **LGI1** display early-onset spontaneous seizures and increase in presynaptic glutamate release (3). It has been reported that assembly of primary cilia in dentate granule cells coincide with formation of glutamatergic synapses from these cells to entorhinal projections which mediate communication between hippocampus and neocortex (4). Dentate granule cells arise from adult hippocampal neurons located in the medial temporal lobe, a region in the brain from which epilepsy may originate, and integrate into existing neural circuits forming functional synapses (4). The novel interaction of **PKD2L1** with **LGI1** may throw light on the role played by cilia in etiology of epilepsy by influencing excitability of neurons.

Asymmetry is observed in structural aspects of the brain such as its cytoarchitecture, gray matter volume and integrity of white matter and in functional aspects of brain, viz. lateralization of cognitive processes such as the dominance of left hemisphere in language and right-handedness (5). This asymmetry which is critical in the functioning of a healthy brain is often reduced in Schizophrenia (6). In Schizophrenia, abnormal asymmetry in functional connections of the brain and disruption of left-hemisphere dominance are observed (6). Abnormalities in brain asymmetry have also been associated with bipolar disorder (7). The ciliary protein, **PKD1L1** (*polycystic kidney disease protein 1-like 1*) which forms a complex with PKD2 (*polycystic kidney disease 2 protein*) in motile cilia of Kupffer’s vesicle, has been shown to be involved in establishing left-right patterning (8). In zebrafish embryos, Kupffer’s vesicle has been previously identified as a ciliated organ which initiates left-right patterning in brain, gut and heart (9). The novel interactor **ABCA13** has been predicted to interact with **PKD1L1** (figure). Cytogenetic disruption, non-synonymous mutations and SNPs from GWAS data have indicated that **ABCA13** (*ATP binding cassette subfamily A member 13*) may be involved in Schizophrenia and bipolar disorder (10, 11). Even though the functions of **ABCA13** are yet to be elucidated, it has been found to be highly expressed in choroid plexus and ciliated ependymal cells lining the ventricles of the brain (10). The novel interaction of **PKD1L1** with **ABCA13** may point at processes underlying brain asymmetry during early stages of development, which may be disrupted in Schizophrenia and bipolar disorder due dysfunction of motile cilia.

Parkinson’s disease is associated with loss of dopaminergic neurons in a region of the brain called substantia nigra leading to loss of dopaminergic input to the striatum (12). A region in the brain of the model organism *Oryzias latipes* (commonly referred to as medaka) called the ventral telencephalon, which is innervated by dopaminergic neurons arising from diencephalon, has been equated in function to the human striatum (13). It has been reported that in medaka, a loss of the gene **PARK2** (*Parkinson protein 2 E3 ubiquitin protein ligase* or *Parkin*) leads to a loss of dopaminergic neurons in the middle diencephalon accompanied by a loss of dopaminergic fibres in the telencephalon (14). Overexpression of PARK2 (Log2FC=1.78, p-value=3.10E-16) was noted in 16 weeks old (fetal stage) diencephalons from right side of female embryos versus Carnegie stage 23 (the last embryonic stage) (15). Mutations in **PARK2** are associated with Parkinson’s disease (16). Loss of **PARK2** activity has been shown to decrease the number of dopaminergic neurons in posterior tuberculum of *Danio rerio* (commonly called zebrafish), a region that has been equated with substantia nigra in humans (13). This decrease in the number of dopaminergic neurons was enhanced on treatment with MPP+, a metabolite of MPTP (*1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine*), which destroys dopaminergic neurons in substantia nigra and is commonly used to induce Parkinson’s disease in animal models (13). It has also been shown that motor deficits and loss of dopaminergic neurons induced by MPTP in mice are rescued by *Parkin*, delivered into the substantia nigra of mice using viral vectors (17). Interestingly, hemi-Parkinsonian rats having unilateral lesions in the dopamine pathway extending from substantia nigra to the striatum were found to have significantly longer neuronal cilia on the lesioned side than on the non-lesioned side (18). Mice injected with Reserpine, a drug that reduces dopamine levels, were found to have elongated neuronal cilia in the striatum and treatment with DRD2 (*dopamine receptor D2* ) agonists reverses this effect (18). Mice lacking DRD2 also exhibited longer neuronal cilia (18). Hence, the novel interaction of the ciliary protein **DYNLT1** with **PARK2** may point at mechanisms controlling the length of cilia on striatal neurons in Parkinson’s disease in which the dopaminergic input from substantia nigra to striatum is disrupted, possibly influenced by the loss of **PARK2** (figure). The cilia gene, **DYNLT1** (*dynein light chain Tctex-type 1*) also known as **Tctex-1**, has been identified as a component of the dynein-2 complex involved in regulating elongation of primary cilia (19). Ciliary length was found to increase when **Tctex-1** was lost following the suppression of dynein heavy chain-2 in retinal pigmented cells, which are used to model normal cilia on neural cells and ciliary defects in ciliopathies (19). Overexpression of DYNLT1 (Log2FC=0.29, p-value=0.0069) was noted in diencephalons from left side of male embryos at Carnegie stage 23 versus Carnegie stage 22 (15).

The novel interaction of **Tctex-1** with **PARK2** may also be relevant in another aspect of Parkinson’s disease etiology, viz. accumulation of the protein alpha-synuclein in lewy bodies. Lewy bodies are inclusion bodies rich in misfolded proteins, found in different regions of the brain of Parkinson’s disease patients (20). Alpha-synuclein accumulates in midbrain dopamine neurons lacking *Parkin*, derived from patient iPSCs (induced pluripotent stem cells) (21). Accumulation of alpha-synuclein has been noted in sub-ependymal and ependymal regions in the brains of Parkinson’s disease patients (22). Ependymal cells are ciliated and line cavities in the brain called ventricles, through which the cerebrospinal fluid flows (23). Ciliary defects in ependymal cells have been linked to development of hydrocephalus (23). It is interesting to note that increased levels of endogenous **Tctex-1** activity and **Tctex-1** promoter or enhancer activity are found in ependymal cells lining the third ventricle (24). It has also been reported that the gene PACRG (*parkin co-regulated gene*) which shares a bidirectional promoter with **PARK2** and also accumulates in lewy bodies of Parkinson’s disease patients, localizes to motile cilia lining the ventricles of the brain, specifically to ciliary axoneme (25). The study demonstrated that in mice, loss of PACRG results in impaired ciliary beating, impaired flow of cerebrospinal fluid mediated by cilia and development of hydrocephalus (25). Hence, the novel interaction of **Tctex-1** with **PARK2**, in this case, may point at processes that influence accumulation of alpha-synuclein in regions of the brain such as the ependyma that has motile cilia, viz. ciliary defects contributing to pathological manifestations of Parkinson’s disease.

## Novel PPIs involved in ciliopathy-associated hydrocephalus

Hydrocephalus is a condition frequently associated with ciliopathies in which cerebrospinal fluid accumulate in the brain ventricle giving rise to an enlarged head (26). While it has been established that defects in adhesion of ependymal cells and formation of cilia may lead to hydrocephalus, the exact mechanisms underlying it are yet to be elucidated (23). The novel interactor **IFITM1** interacting with two ciliary proteins, **NME5** and **DYNLT3**, other novel interactors of NME5, viz. **HBEGF**, **SPOCK1**, **MKRN1**, **APTX**, **VIPR1**, **VDAC1**, **P4HA2**, and the novel interactor **UIMC1** interacting with **DYNLT3** may open up the possibility of multiple factors colluding to cause hydrocephalus- broadly, the dysfunction of cilia in ependymal cells of the brain and a de-regulation of angiogenic factors that influence the formation of vascular lumen (figure). In this respect, loss of cilia among other markers of ependymal cells is observed when VEGF (*vascular endothelial growth factor*)- an inducer of angiogenesis- is infused into the ventricles of the brain, resulting in ventriculomegaly which mimics acquired hydrocephalus (27).

Interestingly, **NME5**, **UIMC1** and **DYNLT3** were predicted as novel interactors for **IFITM1** in our interactome of IFITMs (*interferon-induced transmembrane proteins*) which have been shown to inhibit infection of Zika virus (28).Based on functions of the interacting proteins, a testable hypothesis which linked cilia dysfunction in ependymal cells to microcephaly- a fetal malformation associated with Zika virus infection- was presented in this study (28). Microcephaly is the condition in which the head circumference of newborn babies is below the second percentile for gestation (29). It has previously been suggested that genes implicated in microcephaly may also influence the development of hydrocephalus. For example, ASPM (*abnormal spindle-like microcephaly-associated protein*) which is associated with primary microcephaly and has undergone rapid evolution over the course of recent evolution of hominids is implicated in the size of cerebral cortex and neurogenesis (30). ASH domains that are normally found in proteins localizing to cilia such as *Hydin* and OCRL were also identified in ASPM and this has indicated that ASPM may be involved in cilia dysfunction and hydrocephalus (31). *Hydin* and OCRL have been associated with microcephaly and Lowe oculocerebrorenal syndrome respectively (32, 33). Hence, further investigations into shared mechanisms between development of hydrocephalus and microcephaly in the context of cilia dysfunction are necessary.

**NME5** (*non-metastatic cells 5*) is highly expressed in ependymal cells. In mice homozygous for **NME5**, moderate to marked hydrocephalus along with ciliary dysfunction has been observed (34). **NME5** has been reported to localize within the axoneme in a manner dependent on RIBC2 (*RIB43A domain with coiled-coils 2*), which has been implicated in ciliary motion (35). RIBC2 was predicted here as a novel interactor for ATXN10 (*ataxin 10*), mutations in which were associated with the ciliopathy, nephronophthisis (36). Cytoskeletal events that are guided by VEGF influence formation of vascular lumens (37). It was reported that excess of **HBEGF**- a novel interactor of **NME5**- leads to significant elevation of VEGF and dilation of ventricles, leading to hydrocephalus (38). **HBEGF** (*heparin binding EGF like growth factor*) is known to localize to the ventricular zone and the cortical layer during embryonic development and mediates radial migration in the developing brain (39). HBEGF was found to be overexpressed (Log2FC=2.22, p-value=1.50E-08) in 11 weeks old choroid plexuses of female embryos versus Carnegie stage 23.(15) The choroid plexus, secreting cerebrospinal fluid in the brain, consists of modified, ciliated ependymal cells. **HBEGF** has also been reported to activate eNOS (*endothelial nitric oxide synthase*) which plays a critical role in angiogenesis induced by VEGF and vascular hyperpermeability and is a known interactor of DYNLLI (*dynein light chain LC8-type 1*) in the cilia interactome (40, 41). **IFITM1**, another novel interactor of **NME5**, is expressed in endothelial cells of the bladder, brain and stomach in a manner which is correlated with maturation of blood vessels (42). While being induced during maturation stages of angiogenesis in vitro, in vivo **IFITM1** is stably expressed by microvascular endothelial cells which are quiescent (42). IFITM1 was found to be overexpressed (Log2FC=2.52, p-value=1.10E-09) in 13 weeks old choroid plexuses of female embryos versus Carnegie stage 23 (15). The fact that **IFITM1** (*interferon induced transmembrane protein 1*) was involved in establishing stable contacts between cells during formation of lumen in endothelial tissue was revealed by a study. On knockdown of **IFITM1**, OCLN (occludin) which normally interacts with **IFITM1** and localizes to tight junctions between endothelial cells, is mislocalized as a result of which intercellular vacuoles fail to fuse and form multicellular lumen (42). The mechanism by which **IFITM1** regulates assembly of tight junctions was speculated to be related to endosomal trafficking as it is from recycling endosomes that internalized OCLN is returned to the plasma membrane during remodeling of tight junctions in endothelial cells. **IFITM1** was also predicted as a novel interactor of **DYNLT3** (*dynein light chain Tctex-type 3*) which has been suggested to be associated with dynein 2 (43). *Dynein 2*, which has been associated with human skeletal ciliopathies, is known to be involved in intraflagellar transport (44). Moreover, high expression of *dynein 2* has been observed in ependymal cells (45). Another novel interactor predicted for **DYNLT3** is **UIMC1**. Depletion of **UIMC1** (*ubiquitin interaction motif containing 1*) which occurs in a complex with p73 when overexpressed, impairs translocation of BRCA1 (*breast cancer 1*) to DNA damage sites resulting in defective control of cell cycle and repair of double strand breaks (46, 47). p73 has been implicated in the development and maintenance of ependymal cells and in animals deficient in p73, increased apoptosis and lack of differentiation of RGCs into ependymal cells accompanied by loss of motile cilia resulting in hydrocephalus and hippocampal dysgenesis were reported (48, 49). In a recent study it was observed that p73 is required for establishing translational polarity of the basal body patches on the apical surface of ependymal cells and that disruption of p73 resulting in abnormal translational polarity models human congenital hydrocephalus (50).

Loss of **APTX**, a novel interactor of **NME5**, which is involved in the repair of single stranded DNA, accelerates senescence and delays transcription recovery in cultured cells (51). **APTX** (*aprataxin*) is known to interact with CEP350 (*centrosomal protein 350*) which localizes to the basal body in ciliated cells and is required for ciliogenesis (52). **APTX** also interacts with CNTROB (*centrobin*), a centrosomal protein that is required for the elongation and stability of centrioles (53). Centrosomes assist in assembling primary cilia in quiescent cells (54). Downregulation of the centrosomal protein **VDAC1** (*voltage dependent anion channel 1*) that localizes to the mother centriole gives rise to abnormal ciliogenesis while overexpression of **VDAC1** suppresses cilia formation (55). Low levels of VEGF-A, destructuration of blood vessels and inflammation observed in *Vdac1−/−* RAS MEF tumors also implicate **VDAC1** in vascular development (56). **VDAC1** interacts with several MMPs (*matrix metalloproteinases*) that influence angiogenesis induced by VEGF such as MMP2, MMP3 and MMP14. The expression of MMP2 was significantly higher along with VEGF-A in endothelial cells affected with arteriovenous malformations in the human brain (57). The expression of MMP3 was associated with expression of VEGF-A and its circulating levels in healthy adults (58). The enzymatic activity of MMP14 which interacts with VEGFR1 was found to be necessary for angiogenesis induced by VEFG-A (59). Another novel interactor of **NME5**, **SPOCK1** (*SPARC/osteonectin, Cwcv And Kazal like domains proteoglycan 1*), associated with developmental delay and microcephaly, is strongly expressed in the brain where it modulates neurogenesis and axonal growth during early stages of development (60, 61). SPOCK1 was found to be overexpressed (Log2FC=1.82, p-value=4.60E-10) in 13 weeks old choroid plexuses of female embryos versus Carnegie stage 23 (15). **VIPR1** (*vasoactive intestinal peptide receptor 1*), a novel interactor of **NME5**, has been reported to increase expression of VEGF promoting proliferation of endothelial cells in the vascular tissue of brain via the CAMP/PKA pathway after ischemic insult in vitro (62). **P4HA2** (*prolyl 4-hydroxylase subunit alpha 2*), a novel interactor of **NME5**, is a target gene of the angiogenic process and a hypoxia response gene which was described as the genetic and biochemical link between the p53 tumor suppressor pathway and the synthesis of collagen fragments such as endostatin and tumstatin which are anti-angiogenic (63, 64). The subventricular zone (SVZ) is separated from the cerebrospinal fluid (CSF) flowing inside the lateral ventricles by the layer of ependymal cells that have cilia (65). Both change in the SVZ niche and the integrity of this ependymal boundary are correlated with age (65). Therefore the expression of TERT (*telomerase reverse transcriptase*) that is required for maintaining proliferative capacity of cells is reduced in an age-dependent manner in the SVZ with decreased expression of TERT correlating with decreased neurogenesis in SVZ (66-68). **MKRN1**, a novel interactor of **NME5**, is known to modulate the length of telomeres through proteolysis of TERT which is a known interactor of a ciliary protein DYNLL1 implicated in cell survival, in the cilia interactome (69, 70). **MKRN1** (*Makorin ring finger protein 1*) is also known to interact with MAP1LC3B which is a microtubule-associated protein that localizes to the ciliary axoneme (71).

## Novel PPI involved in primary ciliary dyskinesia

It is known that motile cilia in the respiratory tract participate in mucociliary clearance, i.e. the transport of mucus with trapped microbes and harmful particles away from lungs to protect them from infections and injury (72). In Primary Ciliary Dyskinesia (PCD), a ciliopathy arising from dysfunction of motile cilia and characterized by respiratory tract infections, situs defects and infertility, mucociliary clearance is defective due to cilia dysfunction (73). This leads to recurrent infections in the respiratory tracts of PCD patients (73). Elevated levels of inflammatory cytokines including **IL6** (*interleukin 6*), associated with bacterial infections, have been observed in the nasal cavity of PCD patients (74). **IL6**, which is usually secreted in response to infectious agents or toxic particles, is upregulated in respiratory diseases such as asthma and chronic obstructive pulmonary disease (75). In our interactome, **IL6** has been predicted as a novel interactor of **DNAH11**, which is implicated in PCD (figure). **DNAH11** (*dynein axonemal heavy chain 11*) localizes to the respiratory cilia and mutations in **DNAH11** disrupt the utrastructure of normal cilia and cause hyperkinetic ciliary beating in PCD (76). **IL6** has been identified as a positive regulator of multiciliogenesis during airway repair (77). **IL6** secreted by mesenchymal stromal cells after airway injury activates the STAT3 (*signal transducer and activator of transcription 3*) pathway, promoting regeneration of cells and ciliogenesis by inhibiting the Notch pathway and regulating genes involved in ciliogenesis such as FOXJ1 (77). **IL6** also appears to have an inhibitory effect on beating frequency of cilia in fallopian tubes (78). The novel interaction of **DNAH11** with **IL6** may provide clues to the etiology of respiratory tract defects in PCD, viz. the contribution of inflammatory processes to cilia dysfunction.

## Novel PPIs involved in ciliogenesis

Ciliogenesis and progression of cell cycle are inversely related (79-81). Ciliogenesis has been shown to commence when cells enter their quiescence phase known as G0 phase. On the other hand, cilia are resorbed at the G0/G1 transition phase before cells re-enter the cell cycle and start dividing. The novel interactions of the ciliary protein **CDK3** with **FOXJ1**, **TLK2** and **NAP1L1** may throw light on the cross talk between ciliogenesis and the cell cycle (figure). **CDK3** (*cyclin dependent kinase 3*) promotes exit of cells from their quiescent phase and re-entry into the cell cycle through pRB (*retinoblastoma protein*) phosphorylation (82). **FOXJ1** (*forkhead box J1*), a novel interactor of **CDK3**, is a transcription factor that activates genes involved in ciliogenesis and its activity has been shown to be sufficient for ectopic formation of motile cilia in Xenopus and Zebrafish (83). **TLK2** (*tousled like kinase 2*) regulates the S phase or synthesis phase of the cell cycle by phosphorylating the histone chaperones, ASF1A (*anti-silencing function 1A histone chaperone*) and ASF1B (*anti-silencing function 1B histone chaperone*), which insert histone dimers into newly synthesized DNA (84). **NAP1L1** (*nucleosome assembly protein 1 like 1*) has been reported to be essential for centriole duplication induced by PLK4 (*polo like kinase 4*), a master regulator of centriole formation whose overexpression leads to loss of primary cilia and an increase in the number of proliferating cells (85, 86). It is known that centrioles play an important role in ciliogenesis by acting as basal bodies that give rise to cilia (87).

In early phases of ciliogenesis, actin cytoskeleton has to be re-modeled to form a dense network of actin molecules or an “actin net” at the apical membrane, to allow docking of basal bodies and formation of axonemes (88). It has been shown that RHOA (*ras homolog family member A*) plays an important role in establishing this actin net in ciliated cells (88). **CDK18**, a novel interactor of the ciliary protein **DNAH2**, has been shown to negatively regulate actin cytoskeleton via the FAK/Rho signaling pathway (89). Knockdown of **CDK18** (*cyclin dependent kinase 18*) led to accumulation of actin at the leading edge of HEK293T cells which showed enhanced cell motility and RhoA/Rho-associated kinase activity, while overexpression of **CDK18** led to the formation of filopodia (cellular projections rich in F-actin) in HeLa cells (89, 90). **CDK18** was reported to be upregulated during development of cardiomyocytes from proliferative phases to a stage in which the growth of cardiomyocytes was arrested (91). **CDK18** was also found to be significantly upregulated (log2 FC= 2.0027) in embryoid bodies with beating cardiomyocytes in comparison with embryonic stem cells (92). **CDK18** was found to interact with Cyclin K, which has been found in a complex with CDK13, implicated in syndromic congenital heart disease (93-95). In our interactome, **CDK18** has been predicted to interact with **DNAH2** (*dynein axonemal heavy chain 2*) , a ciliary protein localized to inner arms of the cilium axoneme (96). Hence, the novel interaction of **DNAH2** with **CDK18** may point at processes underlying ciliogenesis during heart development and may also help in unraveling functions of **CDK18** which belongs to the family of highly conserved cyclin-dependent kinases called PCTAIRE kinases that are poorly understood (figure) (97). Since development of heart and brain progresses in tandem sharing common morphogenetic programs, the novel interaction of **DNAH2** with **CDK18** may also point at processes orchestrating ciliogenesis in the brain (98). Interestingly, it was noted from the Human Protein Atlas that **CDK18** had elevated expression in both heart muscle (65.7 transcripts per million) and cerebral cortex (60.7 transcripts per million) (99).

The novel interaction of **ARL6** with the ciliary protein **ARL13B** may be involved in regulating cilia length during ciliogenesis (figure). While overexpression of the ciliary protein implicated in ciliogenesis **ARL13B** (*ADP ribosylation factor like GTPase 13B*) increases cilia length, its loss has been shown to reduce cilia length (100). **ARL6** (*ADP ribosylation factor like GTPase 6*) is a GTP-binding protein mutated in Bardet-Biedl syndrome (101). Proteins that regulate ciliary length have also been shown to be responsible for maintaining protein trafficking in cilia under steady state conditions (102). In this respect, **ARL6** is involved in trafficking proteins of the Bardet-Biedl syndrome complex and also in regulating cilia length (103).

## Novel PPI involved in trafficking of membrane receptors in cilia

BBS proteins, which are implicated in Bardet-Biedl syndrome, have been found to be required for localizing GPCRs to primary cilia on neurons (104). GPCRs (*G protein-coupled receptors*) are membrane receptors that are modulated by >30% of all the drugs that are commercially available (105). The GPCR, **QRFPR** (*pyroglutamylated RFamide peptide receptor*), is a ciliary protein which has been predicted to interact with the novel interactor **BBS12** (figure). **QRFPR** localizes to primary cilia on embryonic hypothalamic neurons in rats and also to cilia on retinal pigmented cells (106). **BBS12** (*Bardet-Biedl syndrome 12*), the novel interactor of **QRFPR**, forms a complex with BBS6 and BBS10 which mediates BBSome assembly (107). **BBS12** also interacts with BBS4 (107). The GPCR, rhodopsin, has been found to accumulate in the cell bodies of photoreceptors in mice lacking BBS4 and BBS6.(108, 109) Two GPCRS, viz. SSTR3 (*somatostatin receptor 3*) and MCHR1 (*melanin concentrating hormone receptor 1*), fail to localize to neuronal cilia in mice lacking BBS4 (104). The novel interaction of **QRFPR** with **BBS12** may open up the possibility of **BBS12** mediating localization of the GPCR, **QRFPR**, into neuronal cilia.

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1. Contributed equally [↑](#footnote-ref-1)