Primary Cilia as a Possible Link between Left-Right Asymmetry and Neurodevelopmental Diseases

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Abstract: Cilia have multiple functions in the development of the entire organism, and participate in the development and functioning of the central nervous system. In the last decade, studies have shown that they are implicated in the development of the visceral left-right asymmetry in different vertebrates. At the same time, some neuropsychiatric disorders, such as schizophrenia, autism, bipolar disorder, and dyslexia, are known to be associated with lateralization failure. In this review, we consider possible links in the mechanisms of determination of visceral asymmetry and brain lateralization, through cilia. We review the functions of seven genes associated with both cilia, and with neurodevelopmental diseases, keeping in mind their possible role in the establishment of the left-right brain asymmetry.

Keywords: schizophrenia; centrosome; left-right asymmetry; Disc1; PCM-1; pericentrin; abelson helper integrator 1; hamartin; DCDC2; Dyx1c1

1. Introduction

Cilia are thin, hair-like structures, projecting from the surface of eukaryotic cells and covered with the cell membrane. Their usual length is 3–15 µm. The cilium consists of the ciliary part (the axoneme protruding from the cell), the basal body, and the transitional zone between the two. The inner part of the basal body serves to maintain its assembly and anchoring.

There are two types of cilia: motile cilia and primary cilia. The functions of motile cilia include cell locomotion and the movement of the fluid surrounding the cell, while primary cilia serve mostly as chemo-, photo-, and mechanosensors [1]. The fundamental difference between these two types of cilia is the absence of the central pair of microtubules in the primary cilium. Although the terms “primary cilium” and “immotile cilium” are often used as synonyms, primary cilium in the central zones of animal embryos can actually move, but unlike motile cilia, they have a rotational pattern of movement. Both motile and primary cilium are necessary for the development and functioning of the nervous system. Motile cilia are only present in a subpopulation of the cells of choroid plexus and in the ependymal cells of brain ventricles. They are essential for cerebrospinal fluid movement [2,3]; the lack of cilia motility can lead to hydrocephalus [4] and prevent migration of some neural progenitors with the cerebrospinal fluid flow [3]. Primary cilium are found in most types of brain cells: neurons, glial cells, neural stem cells, and some cells of choroid plexus. Specialized primary cilium are found in visual, acoustic-vestibular, and olfactory receptors. Several neuromediator receptors (dopamine receptors 1, 2,
and 5, somatostatin receptor 3, and serotonin receptor 6), are expressed in neuronal primary cilia [5]. Moreover, primary cilia act as receptors in morphogen-mediated Shh, and Wnt and Fgf signaling, which are essential for embryonic and adult development of key brain regions, e.g., the hippocampus and cerebellum [6].

More than 1000 ciliary proteins are involved in cilium assembly and functioning [7]. Mutations in their genes lead to defects in cilia, which in turn cause a range of human disorders, referred to as ciliopathies. The first described ciliopathy was the Kartagener syndrome [8,9]. Since then, more than a hundred human disorders have been linked to defects in cilia [7].

Ciliopathies are usually associated with congenital kidney dysfunctions, mental retardation, obesity, hepatic disease, craniofacial defects, retinopathy, polydactyly, and other symptoms. In some cases, ciliopathies are accompanied by situs inversus viscerum. This is due to the fact that cilia are involved in the left-right axis determination [7]. Ciliary beating at the node during the neurula stage leads to the generation of leftward fluid flow, which in turn causes an expression of the genes of the Nodal cascade in the left side of the embryo. Remarkably, the structure of beating cilia in the node is that of primary (9 + 0), not motile (9 + 2), cilia. Since they lack the central pair of microtubules, they have a rotational type of movement, and this rotation produces a left-sided nodal flow.

There are two hypotheses explaining how the fluid flow affects left-sided nodal expression. According to the first theory, the concentration of specific signaling molecules increases in the left side of the embryo due to the fluid flow, and this is sufficient enough to activate the expression of the Nodal signaling cascade [10,11]. The other hypothesis assumes that there are two cilia types in the node: the movable primary cilia, which rotate and generate the fluid flow, and the immotile primary cilia, which serve as mechanoreceptors of the flow; the reception results in a rise of intercellular [Ca^{2+}] [12], which leads to activation of the expression of specific “left-sidedness” genes [13]. The latter hypothesis offers a more convincing explanation of how primary cilia breakdowns cause situs inversus. However, evidence from medaka fish raises a possibility for a mixed mechanism, in which the same motile cilia may serve as both a flow motor, and a chemical sensor of a Nodal cascade triggering molecule [14]. Initially, the involvement of cilia in the left-right patterning was shown for mammalian development [10,11], but the same mechanism has since been hypothesized for other vertebrates [15], and for zebrafish [16] and Xenopus [17], though not for the chick [14,18]. More recent evidence has suggested that a similar mechanism may be involved in ascidians [19].

Asymmetrical Nodal-cascade gene expression is involved, not only in the formation of the normal visceral situs, but also in the establishment of asymmetry in the zebrafish brain, e.g., habenular and parapineal nuclei [20,21]. Moreover, zebrafish of the mutant line fsi (fsi stands for “frequent-situs-inversus”), often demonstrate a concordance between visceral and brain asymmetries, including the partial alteration of the behavioral lateralization [22]. In addition, nodal, lefty, and pitx2 are asymmetrically expressed in the dorsal part of a shark’s brain, but there is no evidence of Nodal cascade participation in the formation of the interhemispheric asymmetry of the telencephalon in mammals [23]. For instance, Broca’s and Wernicke’s areas, responsible for speech in the human and homologous in the ape brain, are located in the left hemisphere, but there is no evidence of a developmental mechanism for this asymmetry. Among people with situs inversus totalis, translocation of speech function from the left hemisphere to the right one is not observed [24]: left-handers are encountered among people with situs inversus as often as among people with situs solitus [25], while the standard dichotic listening test reveals the same results among the people of these two groups [26]. Moreover, language dominance, as revealed by magnetoencephalography and the anatomy of petaia, though not planum temporale, as revealed by magnetic resonance imaging, correlate to situs inversus, suggesting that brain asymmetries might develop via multiple mechanisms [27]. A certain discrepancy between the fish and the human data has not been satisfactorily explained thus far, but since no single gene has been found for the fsi zebrafish line, which would account for the resulting morphological and behavioral phenotypes, it is probable that both genetic and environmental mechanisms are involved. On the other
hand, different developmental mechanisms may result in situs inversus of the inner organs with the same morphology, but not necessarily in the same functional asymmetry of the brain [27–30].

Besides the alterations in visceral left-right asymmetry, defective cilia may also result in the absence of the corpus callosum [6], which plays an important role in the maintenance of interhemispheric crosstalk and functional brain asymmetry, including handedness, bilateral representation of language, functional interhemispheric inhibition, and differences in arousal [31,32]. It is worth noting that an association between relative hand skill and single nucleotide polymorphism (SNP) in a PCSK6 gene, whose product is involved in a Nodal regulation during embryogenesis, was observed in dyslexic patients [33]. However, in the control group, there were no associations that could be explained by epistasis between genes responsible for dyslexia or handedness [33]. Thus, cilia may be involved in different developmental mechanisms, which directly or indirectly influence the asymmetric functions of the human brain, as well as in neurodevelopmental disease. It has been suggested that the lateralization of brain functions confer an evolutionary advantage, by improving the capacity to perform parallel tasks in contralateral brain hemispheres [34]. The left hemisphere is associated with distinguishing various stimuli and focusing attention, whereas the right hemisphere is used to react to danger and express emotions [35]. Therefore, alterations in brain asymmetry can cause impairment in the efficiency of input information processing. A disturbance of the brain asymmetry may correlate with mental disorders: autism [36], dyslexia [37], depression [38], bipolar disorder, and schizophrenia [39,40].

So, on the one hand, cilia defects lead to visceral asymmetry abnormalities, and on the other hand, brain lateralization defects correlate with mental disorders. It is tempting to assume an important role of cilia in the establishment of brain asymmetry, even though there are no direct links between visceral and functional brain asymmetry. There is, however, evidence that visceral asymmetry aberrations, at least in some cases, are comorbid with the disorders listed above: schizophrenia [41–44], depression (and psychotic disorders) [45], and autism [46]. Since we believe that disturbances in brain lateralization can lead to neurodevelopmental diseases, a method which could be used to search for responsible genes would be to check whether neural lateralization and visceral left-right asymmetry have common underlying genetic mechanisms. The genes involved in vertebrate left-right asymmetry establishment may also participate in the lateralization of certain brain regions in Danio rerio [21] and dogfish [23], and eye migration to the side in flatfishes Paralichthys olivaceus and Verasper variegatus [47]. Asymmetric expression of Nodal-cascade proteins in the brain of developing flatfishes has been correlated with the neuronal architecture associated with the alteration of the position of the eyes and orbits [48]. Since cilia are involved in visceral left-right asymmetry in mammals and some other vertebrates, and disturbances in expression of the cilia genes can lead to abnormal left-right asymmetry (e.g., in primary ciliary dyskinesia), we aimed to test the idea that the functions of cilia do affect brain lateralization, and that disturbances of the ciliary structure and function would cause neurodevelopmental diseases. In this review, we explore possible connections between cilia genes and mental disorders, linked with brain laterality defects.

We show that proteins associated with the primary cilia may be involved in neurodevelopmental pathogenesis, and in many cases, influence visceral asymmetry (Table 1). Disrupted in schizophrenia 1 (Disc1), pericentriolar material 1 (PCM-1), and human jouberin (Abelson helper integration site 1 (AHI1)) are linked with schizophrenia, hamartin (Tuberous sclerosis 1 (TSC1)) is linked with autism, and pericentrin (PCNT), DCDC2, and Dyx1c1 are linked with dyslexia. It has been shown that genes, which encode these proteins, are expressed in the central nervous system. Most of these proteins (Disc1, PCM-1, jouberin, and hamartin) are localized in the basal body of the cilia (or in the ciliary transitional zone as jouberin), whilst DCDC2 is an axonemal protein, and Dyx1c1 is localized in both the centrosome and the axonemal part of the primary cilia in some cells (Figure 1).
| Protein | Function in the Cilia | Other Functions | Involvement in Visceral Asymmetry | Associated Psychiatric Disorders | Suggested Mechanisms | Ref. |
|---------|----------------------|----------------|----------------------------------|---------------------------------|---------------------|-----|
| Disc1  | ciliogenesis and intraflagellar transport regulation | microtubular transport, probably mitochondrial protein import machinery, Akt/mTOR and GSK-3/β-catenin/Wnt pathways | neuronal migration, neuronal signaling and signal transduction, axonal bundling, transport of GABA-containing vesicles | schizophrenia, autism, depression, bipolar disorder | [49–54] |
| PCM-1  | ciliogenesis and cilia disassembly | microtubule-based trafficking of proteins to the centrosome, centrosome assembly pericentriolar matrix assembly, anchors the γ-tubulin complex to the centrosome, providing microtubule nucleation sites | cell cycle regulation and migration of neurons alone or in coordination with Disc1 | schizophrenia | [55–58] |
| PCNT   | interacts with proteins involved in cilia assembly | prevention of non-ciliary membrane proteins from diffusing into the ciliary membrane, cilia assembly via interaction with Rab8 | neuronal migration, neuronal signaling and signal transduction, axonal bundling, transport of GABA-containing vesicles | dyslexia schizophrenia | [59–61] |
| AHI1   | ciliogenesis and cilia assembly via interaction with Rab8 | traffic of endocytic vesicles | heart looping in zebrafish knockdown | schizophrenia bipolar disorder | in complex with Hap1 maintains the level of TrkB, neuronal migration | [62–67] |
| TSC1   | inhibits formation of the extra cilia | cell cycle regulation, metabolism, cell polarity, mTOR, PI3K-Akt, the ERK1/2-RSK1 signaling | affected expression of southpaw gene in zebrafish morphants | autism | maintenance of dendrite spine density, mTOR signaling pathway, neuronal migration | [68–71] |
| DCDC2  | ciliogenesis and ciliary signaling | promotes Shh signaling and inhibits Wnt signaling | left-right asymmetry defects in liver, gut, and pancreas | dyslexia | maintenance of the balance between Shh and Wnt signaling, neuronal migration | [13,42,72] |
| DYSX1C1| ciliogenesis and cilia motility (dynein arm assembly) | normal heart looping, left-right asymmetry defects in liver, gut, and pancreas | dyslexia | neuronal migration | [73–76] |
Within this family, one third of the family members suffered from mental and/or behavioral disorders [77], including schizophrenia, schizoaffective disorder, and bipolar affective disorder. It was later identified that this translocation resulted in the breakdown of a gene, which was named disrupted in schizophrenia 1 [78]. More than 10 years of studies focusing on disc1 in various populations, have established its involvement in a number of psychiatric diseases: autism [79], depression [80,81], bipolar disorder [82–84], and schizophrenia [78]. Disc1 has many binding partners and is thus involved in many physiological processes. Its mutations, or a disturbance of its expression, lead to their breakdown.

Within the cell, Disc1 is located in several cell compartments, including the nucleus, centrosome, microtubules, and mitochondria. Disc1 is localized near the base of immotile cilia in the cultured NIH3T3 cells and rat striatal neurons. It is essential for primary cilia formation; knockdown of this gene results in the loss of immotile cilia, and in a decrease of dopamine receptors on the cell surface [49]. A defect in ciliogenesis, caused by mouse disc1 suppression, could be rescued by human Disc1 in NIH3T3 [49]. Moreover, Disc1 is probably involved in intraflagellar transport regulation, because it interacts with MIPT3 (microtubule-interacting protein associated with TNF receptor associated factor-3) [50], which is crucial in forming intraflagellar transport particle complexes [51].

In addition to its role in the formation of primary cilia, Disc1 is involved in plus-end and minus-end microtubular transport: Disc1 interacts with microtubule motor proteins, dynein intermediate chain (DyntC) and Kinesin-1. Taking into consideration the fact that Disc1 can interact with a wide range of cellular proteins, it has been suggested that Disc1 is required for the transport of various cargoes as an adaptor, and helps to attach them to microtubule motor proteins [86].

During neurogenesis, an accurate position of the centrosome is important for neuronal cell migration and for determining the fate of the daughter cell (i.e., a cell’s decision to be differentiated into a neuron or to remain as a progenitor cell) [87]. In cortical neurons, Disc1 is co-localized with γ-tubulin and is required for the assembly of centriole [88]. Disc1 can interact with multiple proteins of the centrosome, anchoring the dynein motor complex to the centrosome. Based on this fact, it is suggested that disc1 expression in neuronal cells is crucial for neuronal development and migration. disc1 knockdown disconnects the nucleus and centrosome during cell migration, which results in an abnormal development of the cerebral cortex [88].

The ability of Disc1 to interact with the intracellular transport proteins makes it a significant factor in the functioning of the nervous system. Disc1 is involved in neurite outgrowth [89], and regulates the...
structure and functioning of the synapses [90]. Since Disc1 knockdown inhibits microtubule-associated cellular transport of various cargoes, it probably participates in both anterograde and retrograde transport, through the axon [5]. Moreover, Disc1 is a key factor in the development of the central nervous system. Besides regulating neuronal cell migration, it also regulates neural cell proliferation, e.g., cortical progenitors in utero and in adults [91]. In both humans and rodents, disc1 expression is the highest during the developmental stages of the central nervous system, after which it gradually decreases [92].

Disc1 interacts with girdin [93] and β-catenin [91], and participates in Akt/mTOR, GSK-3/β-catenin, and Wnt signaling, which are all involved in neurogenesis and adult neurodevelopment. Moreover, Disc1 is connected to several pathways of neuronal signal transduction, including PDE4/cAMP [94], GABA [95], and dopamine [49] mediated pathways. Mutations in disc1 alter the intracellular GABA transport [51,96]. Some of these pathways, e.g., GSK-3/β-catenin, are related to neurodevelopmental disorders, such as schizophrenia [97–99].

In sum, Disc1 is involved in the development and functioning of the nervous system and, as an interactor with a set of proteins, is responsible for various neural cell functions. Mutations in disc1 result in mental disorders, such as autism, depression, bipolar disorder, and schizophrenia. However, these mental dysfunctions are caused by Disc1 deficit, and are not associated with cilia dysfunctions. For example, Disc1 is also located in mitochondria, which are involved in some human diseases of the central nervous system, including schizophrenia and bipolar disorder [52].

3. Pericentriolar Material (PCM-1)

Pericentriolar material 1 is a protein, which was initially described in HeLa cells as being associated with the centrosomes in the interphase, and dispersed throughout the cell during the rest of the cell cycle [100]. The gene pcm-1 is located on chromosome 8. Later, it was shown that PCM-1 is a component of centriolar satellites [101], small non-membranous 70–100 nm particles, which surround the centrosome; similar structures also exist around the basal bodies in ciliated cells. During induced ciliogenesis in murine nasal respiratory epithelial cells, the content of PCM-1 in the apical cytoplasm increased [101]. PCM-1 has coiled-coil domains underlying its ability to undergo oligomerization [102] and interaction with other proteins.

PCM-1 is reported to contribute to the dynein-dependent, microtubule-based trafficking of proteins to the centrosome [55]. It makes complexes with itself, Disc1, and BBS4 (Bardet-Biedl syndrome 4) [56], which can bind cargo proteins to dynein. PCM-1 is crucial for the assembly of the centrosomal proteins centrin, pericentrin, and ninein at the centrosome; the organization of a radial microtubule network depends on PCM-1, and depletion of PCM-1 inhibits anchorage of microtubules to the centrosome [55]. It is worth noting that depletion of the centriolar satellite protein PCM-1 has no effect on centriole assembly, but reduces the amount of centrosomal proteins at basal bodies [103].

PCM-1 is also thought to be critical for flagella assembly. In pcm-1 zebrafish morphants, the cilia in pronephros were reduced in length, which was correlated with the dose of morpholino used in the experiment. In morphant embryos, cilia within the Kupffer’s vesicle were less than half as long as in controls, which led to inverted heart looping, consistent with randomization of left–right asymmetry [104].

PCM-1 is probably involved in cilia assembly by interaction with proteins such as BBS4, CEP290 [105,106], and OFD1 [107]. Complex PCM-1-CEP290 is pivotal to targeting Rab8 to promote ciliogenesis. In this way, PCM-1 function is required for the formation of the non-motile primary cilium [105]. Also, PCM-1 regulates ciliogenesis through interacting with Htt, whose depletion leads to dispersion of PCM-1 satellites and impairs primary ciliary formation [106].

PCM-1 takes part in cilia disassembly before mitosis. Polo-like kinase 1 (Plk1) promotes primary cilia resorption by activating histone deacetylase 6 (HDAC6), a tubulin deacetylase which is responsible for modulating cell spreading and motility, as well as primary cilia resorption. Along with the latter
process, during mitotic G2 phase, Plk1 is accumulated around the pericentriolar matrix, where its recruitment is carried out by PCM-1, phosphorylated by CDK1 [57].

Interestingly, PCM-1 interacts with Disc1, and localization of PCM-1 in the centrosome is regulated by this interaction. An allelic variant of Disc1, which is associated with schizophrenia-related phenotypes, Leu607Phe, and an allelic variant Ser704Cys, affects the PCM-1 distribution in the centrosome [108,109].

In the developing cerebral cortex, suppression of PCM-1 leads to neuronal migration defects [56]. Population studies in the United Kingdom have demonstrated that pcm-1 is implicated in susceptibility to schizophrenia [110]. SNP rs370429 in pcm-1, which causes the isoleucine to change to threonine, has also been shown to be associated with schizophrenia. Among the 98 carriers of rs370429, 67 were affected by schizophrenia [111]. However, investigations in Japanese populations have not revealed any linkages between pcm-1 and schizophrenia [112,113]. In animal experiments, pcm-1+/− mice demonstrate behavioral abnormalities, impairment in social interactions, and significantly reduced activity in the open field. However, mutant mice behave normally in the elevated plus maze, rotarod, prepulse inhibition, and progressive ratio tests [114].

4. Pericentrin (PCNT)

Pericentrin (PCNT) is also known as kendrin. This protein is constitutively localized in the microtubule-organizing center and is indispensable for the assembly of the pericentriolar matrix [59,60]. PCNT is localized in basal bodies and interacts with proteins involved in cilia assembly; pcnt silencing causes the inhibition of primary cilia formation [115]. An increased expression of PCNT in the postmortem brains and in the peripheral blood lymphocytes of bipolar disorder patients, when compared to healthy controls, has been demonstrated, although no SNP in PCNT associated with bipolar disorder were found [116]. However, the same team found significant allelic and genotypic associations of PCNT with schizophrenia in a Japanese population [117]. Differences in allelic frequencies or genotypic distributions of PCNT SNPs, between controls and schizophrenia patients, however, were not found in other studies [118]. Nevertheless, it was established that mutations in the pcnt lead to abnormal interneuron migration in the murine olfactory bulb, whereas schizophrenia is known to be accompanied by reduced olfactory bulb volume [61]. Pericentrin also interacts with Disc1 [119] and PCM-1 [55], which are essential for the keeping the central nervous system in a healthy condition, and in diseases. PCNT might also be important for susceptibility to dyslexia, because PCNT is localized on the chromosome region 21q22.3, and a deletion in this region was associated with dyslexia in the case of a dyslectic father and his three sons [120].

5. Abelson Helper Integration Site 1 (AHI1)

AHI1 (abelson helper integration site 1) is a cytoplasmic protein. AHI1 is associated with Joubert syndrome [121,122], otherwise known as jouberin. Mutations in AHI1 are identified in 12% of patients with Joubert syndrome [123]. In a cell, AHI1 is localized in the transitional zone. It is involved in a protein complex, which serves as a barrier for non-ciliary-membrane proteins, preventing them from diffusing into the ciliary membrane [62].

The murine orthologue of AHI1 regulates cilia assembly via interaction with Rab8a: in mouse ahi1-knockdown cells, the ciliogenesis was impaired, and Rab8a was destabilized and did not properly localize to the basal body. Moreover, defects in the trafficking of endocytic vesicles from the plasma membrane to the Golgi complex and back to the plasma membrane were observed in ahi1-knockdown cells [63]. Interestingly, another cilia-associated protein PCM-1 is also involved in cilia formation via interaction with CEP290, whose complex CEP290–PCM-1 targets Rab8a in ciliogenesis [105]. It remains unknown whether PCM-1 and AHI1 work cooperatively in recruiting the Rab8a in ciliogenesis, or through different mechanisms.

So, as AHI1 is a pivotal protein for cilia formation and function, the knockdown of ahi1 leads to the impairment of ciliogenesis. Reportedly, ahi1 knockdown causes developmental abnormalities.
For instance, in \textit{ahi1} knockdown zebrafish, the loss of cilia in the Kupffer’s vesicle, and subsequent defects in cardiac left–right asymmetry, were demonstrated [64].

\textit{AHII} interacts with \(\beta\)-catenin and facilitates its accumulation in the nucleus, positively modulating Wnt signaling [124]. In ciliated murine embryonic fibroblasts, the nuclear level of \textit{AHII} and \(\beta\)-catenin is reduced in comparison to cells bearing primary cilia, i.e., nonmotile cilia disturb canonical Wnt signaling through a compartmentalization of its components. This repressive regulation does not silence the pathway, but maintains a discrete range of Wnt responsiveness; cells without cilia potentiate Wnt responses, whereas in cells with more than one cilium, responses are inhibited [125].

Mouse \textit{Ahi1} forms a stable complex with huntingtin-associated protein 1 (Hap1), which is involved in intracellular trafficking and is pivotal for neonatal development. The altered expression of \textit{hap1} causes a reduced \textit{Ahi1} level, and vice versa, \textit{ahi1} deficiency reduces the level of \textit{Hap1} [126]. Hap1 and Ahi1 stabilize each other, and are important for maintaining the level of tyrosine kinase receptor B (TrkB) [126], whose signaling seems to be critical in the risk of depression and bipolar disorder [65], and pivotal for brain development [126]. Interaction with HAP1 is also established for another cilia basal body associated protein, PCM-1, whose depletion leads to the impairment of primary cilium formation [106].

\textit{AHII} is expressed in the adult brain of both rodents and humans [126–128]. People with Joubert syndrome are characterized by abnormalities of the brainstem and cerebellum, weakness, clumsiness, and cognitive difficulties [121,129]. Brain polarity-associated disorders are shown to be associated with \textit{AHII} gene alteration. Potential evidence of the association between some variants of \textit{AHII} and bipolar disorder susceptibility has been reported, but no connections with clinical outcomes were revealed [65].

Connections between \textit{AHII} and schizophrenia vulnerability were established in several studies in various populations [130–133]. Moreover, a possible link between an \textit{AHII} SNP and a clinical outcome in patients with schizophrenia was found [134]. However, no differences in brain expression of \textit{AHII} in patients with schizophrenia or bipolar disorder, when compared to healthy people, were revealed [135].

6. Hamartin (Tuberous Sclerosis 1—TSC1)

The \textit{TSC1} gene encodes hamartin. Mutations in this gene are associated with tuberous sclerosis, also known as tuberous sclerosis complex (TSC); hence the gene was named \textit{tuberous sclerosis-1} and the protein name hamartin is from the hamartias, distinctive tumor-like malformations in a wide range of human tissues, characterizing the physical manifestation of this disease [136]. Patients with tuberous sclerosis often develop multiple tumors and it has been suggested that the \textit{TSC1} is a tumor suppressor. Overexpression of \textit{TSC1} leads to both cell growth inhibition and cell morphology changes [137]. The growth inhibition is associated with an increase in the endogenous level of tuberin, a product of the \textit{TSC2} gene. A complex with hamartin-stabilized tuberin saved both proteins from ubiquitination, resulting in cell growth inhibition [137].

The hamartin-tuberin complex can also inhibit the mammalian target of rapamycin (mTOR) signaling, resulting in the inhibition of translational initiator S6 kinase 1 and of the inhibitor of translational initiation 4E binding protein 1 [138]. Acting as a GTPase-activating protein in the Rheb complex, hamartin-tuberin regulate mTOR; a lack of hamartin or tuberin causes an increase of Rheb-GTPs, which, in turn, causes a constitutive activation of mTOR signaling. This results in deregulation of the cell cycle and gene expression [139].

Hamartin is localized to the centrosome and can interact with the mitotic kinase Plk1. \textit{tsc1}\(-/-\) murine embryonic fibroblasts show an increased number of centrosomes, when compared to \textit{tsc1}+/+ cells [140]. Besides the centrosome, hamartin is localized in the basal body of the primary cilium. The loss of hamartin enhances ciliary formation: murine embryonic fibroblasts from \textit{tsc1}\(-/-\) animals had a higher quantity of ciliated cells, than cells from control \textit{tsc1}+/+ mice [68]. Disturbances in \textit{tsc1} expression cause a difference in cilia length [68,141]. Furthermore, mice with a broken-down \textit{tsc1} gene
exhibited a significant reduction in dendritic spine density, in comparison with neuronal dendrites from control mice [69].

Two tsc1 homologs, referred to as tsc1a and tsc1b, were found in zebrafish. In tsc1a knockdown fish, elongation of cilia, and defects in left-right visceral asymmetry, were observed. Moreover, kidney cyst formation in ciliary mutants was blocked by the TOR inhibitor, rapamycin [70].

Altogether, hamartin, or the hamartin−tuberin complex, interacts with more than 50 proteins. Besides tuberin, hamartin also forms complexes with proteins: DOCK7, ezrin/radixin/moesin, FIP200, IKKb, Melted, Merlin, NADE (p75NTR), NF-L, Plk1, and TBC7. It has not been shown whether the proteins interacting with hamartin also form complexes with tuberin, apart from Plk1 and TBC7, which are known not to interact with tuberin [71]. The hamartin−tuberin complex is involved in at least three signaling pathways: the PI3K-Akt pathway, the ERK1/2-RSK1 pathway, and the LKB1-AMPK pathway. So, hamartin-tuberin is recruited in the cell cycle, metabolism, and cell polarity control. Acting in the brain, the hamartin-tuberin complex is involved in neuronal arborization, which constitutes the regulation of spine density as a part of the PI3K-Akt-mTOR pathway [142].

A characteristic feature of patients with tuberous sclerosis is autism [143–145]. Heterozygous or homozygous loss of tsc1 in murine cerebellar Purkinje cells, leads to autistic-like behaviors, including abnormal social interaction, repetitive behavior, and vocalizations, while treatment with rapamycin abolishes this misbehavior [146]. The hamartin-tuberin complex also negatively regulates β-catenin stability and activity, by participating in β-catenin degradation complex [147]. It is suggested that the activity of the canonical Wnt pathway is altered, at least in a subset of patients, with autism spectrum disorder [148].

7. DCDC2

While its function remains undisclosed, DCDC2 has been shown to be associated with dyslexia [149,150]. DCDC2 is expressed in the fetal and adult human CNS [150]. It is localized to the brain regions which are active at the time of cursory reading. DCDC2 belongs to the doublecortin family, which is characterized by an ability to bind microtubules and by an involvement in neuronal migration [72]. dcdc2 silencing in rat embryos results in an impairment of neuronal migration [149]. The DCDC2 protein is localized to the primary cilium axoneme and its overexpression results in cilia length enhancement [72,151]. When dcd2 is overexpressed in rat hippocampal cells, an aberrant morphology of neurite outgrowth is observed: the branching of neurites increases, although their total length does not change significantly [72]. A knockdown of dcd2 disrupts ciliogenesis in a murine kidney cell line IMCD-3, but ciliogenesis in affected cells may be rescued by artificially-induced wild-type human DCDC2 expression [151]. Animal studies revealed that dcd2 mutations cause a renal-hepatic ciliopathy in murine models and lead to ciliopathy phenotypes in zebrafish [151]. dcd2 zebrafish orthologue is also involved in left-right patterning [151].

DCDC2 is involved in ciliary signaling: an overexpression of dcd2 triggers Shh signaling, whereas dcd2 downregulation by shRNA, leads to Wnt signaling [72,151]. DCDC2 interacts with disheveled proteins 1–3, while DCDC2 overexpression represses β-catenin-dependent Wnt signaling [151]. Zebrafish ciliopathy phenotype in dcd2 morphants can be rescued by the addition of a β-catenin inhibitor [151]. In addition, DCDC2 is localized in the kinocilia of sensory hair cells and the primary cilia of nonsensory supporting cells. A missense mutation in DCDC2 caused deafness in a Tunisian family [152]. Although DCDC2 was described as a susceptibility gene for dyslexia in the United States [149], Germany [150], and Italy [153], studies in a UK population have only revealed weak, inconsistent evidence for DCDC2 involvement in dyslexia [154]. Moreover, a linkage between DCDC2 SNPs and gray matter volumes in the superior prefrontal, temporal, and occipital networks (regions including multiple reading and language-related areas), has been found; linkages were observed in subjects with schizophrenia, but not in the control group [155]. An association between the SNPs rs793842 and rs3743204 (in DCDC2 and dyx1c1 genes respectively), and the volume of the white matter
in the left temporo-parietal region, was also shown. Although an association between the white matter volume and reading scores was found, these SNPs did not appear to be linked with reading skills [156]. Considering that mutations in doublecortin genes lead to neuronal migration impairment, and RNA knockdown disturbs neuron progenitors migration in rat embryos [149], it has been suggested that defects in the DCDC2 gene cause dyslexia by means of incorrect migration of neural progenitor cells.

8. DYX1C1

The Dyx1c1 gene is involved in dyslexia; its expression in a set of cortical neurons and glial cells occurs in white matter [157]. Based on a large set of published microarray data, it has been suggested that Dyx1c1 belongs to ciliary proteins [158]. In the primary cilia of some cells, the Dyx1c1-GFP fusion protein was co-localized with γ-tubulin at the centrosome, and in some other cells, in a primary cilia axoneme [159].

As shown by the use of mRNA in in situ hybridization, dyx1c1 is expressed in many ciliated tissues in zebrafish, both adult and fetal. In dyx1c1 morphants, cilia length is reduced in several organs, including the Kupffer’s vesicle [73]. Furthermore, the loss of both outer and inner dynein arms, which are required for cilia motility, was detected in dyx1c1 morphants [73]. The defects in dynein arms were found in primary ciliary dyskinesia patients bearing a mutation in dyx1c1 [74]. A loss-of-function of dyx1c1 in zebrafish also causes aberrations in organ asymmetry: heart looping, coiling of the gut, position of the liver, and the breakdown of the pancreas. Additionally, the position of the parapineal organ was reversed in a part of dyx1c1 morphant embryos [73,74]. Moreover, Tarkar and colleagues found the situs inversus phenotype in five out of 12 primary ciliary dyskinesia patients with recessive mutations in dyx1c1, and two individuals had aberrations in left-right asymmetry (one with dextrocardia and polysplenia, and one with left atrial isomerism and polysplenia) [74].

The association between some Dyx1c1 SNPs and dyslexia has been recorded in various populations [160–162]. Animal studies have shown that mice with the homozygous Dyx1c1 knockout, demonstrate memory and learning deficits [163]. In utero knockdown of Dyx1c1, disrupted neuronal migration has been recorded in the developing neocortex of rat embryos [75,76]. Neuronal migration abnormalities were also observed in the brains of dyslexic patients [76].

9. General Discussion

When starting this review, we expected to demonstrate some linkage between ciliary proteins and neurodevelopmental disorders, based on an involvement of primary cilia in the development of brain asymmetry. However, we failed to find any evidence to confirm this hypothesis. Although these proteins are associated with primary cilia, they affect neurodevelopmental disorders by other mechanisms. The way in which aberrations in gene expression lead to behavior impairment, is still not entirely clear. There are several ways in which the proteins reviewed here can influence the development of mental disorders: by affecting neuronal migration, by influencing neurites outgrowth, or by alternating cellular and interneuron signaling (Table 1). Alterations in the expression of the ciliary proteins lead to incorrect neuronal migration (Table 1), which is a crucial event for the formation of the cerebral cortex. Mental retardation or cognitive defects are observed in some ciliopathies [164,165], suggesting that cilia are important for brain development and functioning. Aberrations of neuronal precursor cell migration are known in schizophrenia [166], autism [167], bipolar disorder [168], and dyslexia [169], although there is also conflicting evidence for this [170]. For example, incorrect neuronal migration, caused by a Disc1 single-nucleotide polymorphism, leads to a deficiency in the grey matter volume in some brain areas in patients with major depressive disorders [80], while that caused by polymorphisms in dyx1c1 or dcdc2, leads to changes in temporo-parietal white matter structure [156]. Disc1, PCM-1, PCNT, and TSC1 are located, and have functions in, the centrosome (Table 1). This organelle, as the main microtubular cytoskeleton organizing center, is implicated in various processes during the development of the
nervous system, particularly in neuronal migration and polarization [171]. Thus, mutations in the
genes coding the proteins under review result in incorrect functioning of the centrosome. This may,
in turn, lead to neurodevelopmental disorders, probably via incorrect neuronal precursor migration.

Apart from neuronal migration, centrosomes are involved in neurite growth and branching. Its incorrect functioning, therefore, reflects breakages in interrelations of neurons by disturbance of neuritis and incorrect spindle orientation [172]. In a recent study, the dendrite arborization was shown to depend on normal ciliogenesis: disruption of normal ciliogenesis impaired dendrite outgrowth [173]. An alteration of the expression of ciliary protein genes causes a disturbance of the neurite net. Disc1 is involved in the neurite outgrowth [89]. Other proteins are also implicated in the neuronal net construction: aberrations in the expression of disc1 and tsc1 causes a decrease in dendritic spines [69,174], while an overexpression of dcdc2 leads to an increase in neurite branching [72], and the expression of truncated ahi1 results in inhibition of neurite outgrowth [126]. Breakages in the function of cilia genes lead to aberrant brain development, which causes functional and structural brain abnormalities, observed, e.g., in schizophrenic [175,176], autistic [177], and dyslexic [156] patients.

Furthermore, Disc1 is recruited in GABA_A-R-trafficking in cortical neurons, via its involvement in microtubule-associated cellular transport: its knockdown or overexpression alters distribution of GABA_A-R on the neuron’s surface [96]. Mutations in disc1 lead to the reduction of released GABA, due to alterations of cellular traffic [51]. Disc1 regulates dendrite development during adult neurogenesis and this regulation requires GABA-induced depolarization, through a convergence with the AKT-mTOR pathway [95]. Recruitment of mTOR signaling leads to speculation that TSC1 is involved in GABA signaling. Indeed, in conditional knockout mice with deletion of the tsc1 gene in GABAergic interneuron progenitor cells, the number of GABAergic neurons in the cortex and the dentate gyrus, was decreased; moreover, the upregulation of mTORC1 signaling and increased GABAergic interneuron size were observed [178]. Hap1, the binding partner of PCM-1, TSC1, and AHI1, is implicated in the rapid delivery of GABA_A-Rs to inhibitory synapses [179]. Also, dxy1c1 knockdown in utero causes a non-cell autonomous effect on GABAergic neuronal migration [180]. So, GABA is another way by which defects in ciliary proteins can provoke mental disorders. GABA is the key inhibitory neurotransmitter involved in hyperpolarization of the neurons. It is also an important mediator in the regulation of adult neurogenesis, being involved in proliferation, migration, and synaptic integration of the neurons [181]. Aberrations of the GABA-pathway are associated with neural disorders, such as schizophrenia [182,183], bipolar disorder [184], and autism [185].

Primary cilia are implicated in some paracrine signaling pathways. In particular, cilia play
crucial roles in hedgehog and wnt signaling [1], i.e., in signaling pathways that take part in
neurogenesis [58,186,187], and whose failures are associated with neurodevelopmental diseases [148,188].
For the majority of the considered proteins, a direct involvement in these signaling pathways has been
shown (Table 1).

The known relations between reviewed proteins are presented in Figure 2, and their associations
to neurodevelopmental disease are schematized in Figure 3. Disc1 can contact PCM-1 and PCNT.
Each of these three proteins has been shown to be associated with schizophrenia. It is unknown,
however, whether PCNT, Disc1, and PCM-1, act independently or in an orchestrated manner in
neurodevelopmental disorders. Disturbance in this complex may affect cell division in the central
nervous system. This proposition is supported by the finding that PCM-1-associated schizophrenia
patients have orbitofrontal volumetric deficits [110]. PCM-1 and AHI1 can interact with Rab8 and Plk1.
However, although PCM-1 and AHI1 are associated with schizophrenia, there are no observations of
implication of either Plk1 or Rab8, into pathogenesis of schizophrenia.
TSC1 and Disc1 interact with 14-3-3 proteins. 14-3-3 proteins are a family of regulatory proteins, involved in cell cycle regulation and apoptosis [189]. They express during development and in adulthood. There is evidence that disturbances in the quantities of these proteins in the cell, are implicated in neurological disorders with polarity breakdown: autism [190–192], bipolar disorder [193,194], and schizophrenia [195,196]. Interestingly, 14-3-3 proteins are recruited in vertebrate left-right axis determination [197]. The TSC1-TSC2 complex is capable of interacting with all proteins from the 14-3-3 family. There is no evidence of direct interaction of TSC1 with 14-3-3 proteins, but it is likely that the interaction is carried out through TSC2. The binding of the 14-3-3 protein to the TSC1-TSC2 complex prevents an inhibition of S6 kinase and the non-phosphorylation of 4E binding protein 1, i.e., it causes a weakening of the PI3K/PKB/TOR pathway signaling [198]. Conversely, cellular levels of some 14-3-3 proteins (γ, ε, σ, and ζ) are regulated by TSC1 and TSC2 [199]. Disc1
can also interact with 14-3-3 proteins, in particular, with 14-3-3ζ [200] and 14-3-3ε [201]. While 14-3-3 proteins and Disc-1 are known to be associated with schizophrenia, no such evidence exists for TSC1.

Another common partner of Disc-1 and hamartin, is RASSF7, a member of a family of Ras association domain–containing proteins (RASSF). It is a centrosomal protein. Its knockdown in Xenopus causes nuclear breakdown, apoptosis, and a striking loss of tissue architecture in the neural tube [202], but its associations with neurodevelopmental disorders, with which Disc-1 or TSC1 have linkages, are still unknown. Futhermore, no connections between DCDC2 and Dyx1c1, or with other ciliary proteins, have been revealed.

On the one hand, the majority of the considered ciliary proteins affect visceral left-right asymmetry (Table 1), whereas mental disorders are associated with failures in laterization. On the other hand, there is no direct evidence that these proteins are involved in neuropathological processes through the mechanisms underlying visceral asymmetry. Therefore, a divergence in developmental mechanisms underlying the establishment of visceral and brain asymmetries can be suggested [27–29]. This view is supported by a recent finding by Vingerhoets and colleagues [203], that only situs inversus totalis patients with ciliopathies preserve sidedness of the neurobehavioural phenotypes. In contrast, those patients with situs inversus totalis, who express no symptoms of ciliopathies, display a tendency to randomize neurobehavioural asymmetries, suggesting that two different developmental mechanisms underlie visceral situs. All these data explain why ciliary proteins may be associated with both mental disorders and visceral asymmetries, but the patients may not necessarily express both psychiatric and inverted visceral phenotypes. They also indicate why mental disorders and visceral inversions may be related to ciliary (no doubt, various) malfunctions, but not necessarily to left-right neurobehavioural asymmetries, at the same time [203]. Since disturbances in ciliary genes lead to mental disorders, we can expect that findings of other ciliary genes, specifically of their mutations, will indicate that they may lead to psychiatry phenotypes.

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