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Review Article

Anatomy-informed Modeling of Human Ciliopathy with Brain Organoids

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Abstract : Brain organoids offer unprecedented opportunities to model human neurodevelopment in a three-dimensional, anatomically relevant context. In this review, we focus on ciliopathies, such as Joubert and Meckel-Gruber syndromes, which represent a group of neurodevelopmental disorders characterized by overt anatomical malformations including disrupted ventricular organization, midline defects, and cerebellar hypoplasia. These conditions underscore the central role of primary cilia in orchestrating spatial patterning and morphogenesis of the human brain. Building on this anatomical framework, we discuss how brain organoids, by self-organizing into regionally specified, polarity-maintained structures, serve as powerful platforms to investigate the developmental consequences of ciliary dysfunction in a human-specific manner. Notably, this review synthesizes recent organoid-based models of key ciliopathy-related genes, such as RPGRIP1L, INPP5E, and ARL13B, and demonstrates how each mutation leads to distinct disruptions in rostro-caudal or dorsoventral brain patterning. These structural phenotypes, often undetectable in animal models, underscore the added value of organoids in modeling human ciliopathies. By integrating insights from developmental neurobiology with an anatomical perspective, this review provides a structurally grounded lens to interpret the pathogenesis of ciliopathy and underscores the emerging utility of brain organoids as both mechanistic and morphological disease models.

Keywords : Brain development, Ciliopathy, Primary cilia, Brain organoid

INTRODUCTION

Neurodevelopmental disorders encompass a broad range of conditions arising from disruptions in early brain development [1]. Among them, ciliopathies represent a unique category of disorders that exhibit clearly defined anatomical malformations, offering a rare opportunity to connect molecular dysfunction with observable structural defects [2,3]. These disorders, which include Joubert syndrome, Meckel-Gruber syndrome, and Bardet-Biedl syndrome, are caused by mutations in genes regulating the structure and function of primary cilia, specialized organelles that play essential roles in morphogen signaling, cell polarity, and tissue organization [4-8].

The central nervous system is particularly vulnerable to ciliary dysfunction, as primary cilia are highly enriched on neuroepithelial cells lining the ventricular zone and are essential for orchestrating spatial patterning during early

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corticogenesis [9-11]. Ciliopathies often present with cerebellar vermis hypoplasia, ventricular enlargement, corpus callosum agenesis, and midline brainstem defects, anatomical hallmarks that underscore the pivotal role of cilia in shaping human brain structure [10,12,13]. While animal models have contributed significantly to our understanding of ciliary biology, species-specific differences in brain architecture, such as the absence of gyrification and simplified ventricular systems in rodents, have limited their capacity to model the full spectrum of human ciliopathy phenotypes [14-19]. In this review, we use the term 'primary cilia dysfunction' to refer to structural or compositional defects of the cilium itself, while 'ciliary signaling defect' denotes downstream disruptions in pathways such as SHH that arise due to impaired ciliary signal transduction.

Recent advances in brain organoid technology offer a promising alternative. Brain organoids derived from human pluripotent stem cells self-organize into radially patterned structures that recapitulate ventricular zone architecture, neuroepithelial polarity, and early regional identity [20-22]. These features make organoids particularly suited for anatomically grounded investigation of developmental disorders that affect tissue structure. In this review, we focus on the application of brain organoid models to the study of human ciliopathies. By integrating insights from developmental biology and neuroanatomy, we highlight how this platform enables a deeper understanding of how disruptions in ciliary function lead to human-specific malformations in the developing brain (Table 1).

PRIMARY CILIA IN EARLY BRAIN MORPHOGENESIS AND CILIOPATHY-ASSOCIATED STRUCTURAL DEFECTS

Primary cilia are solitary, non-motile organelles that extend from the apical surface of most vertebrate cells [2].

Table 1. Glossary of key neuroanatomical terms frequently used in ciliopathy research and their relevance in brain organoid models

Term	Definition	Relevance to ciliopathy
Ventricular zone	A proliferative layer lining the brain's ventricles composed of neural progenitor cells responsible for early neurogenesis.	Ciliary dysfunction disrupts neural progenitor proliferation in this region, leading to ventricular abnormalities such as ventriculomegaly [9,26,27].
Apical polarity	The structural organization of epithelial cells with distinct apical and basal surfaces, crucial for maintaining lumen integrity and directed cell division.	Loss of apical polarity is a key structural phenotype in cilia-deficient organoids and reflects disrupted epithelial organization [9,26,27].
Radial glia	Bipolar neural progenitor cells that span from the ventricular surface to the pial surface and guide migration of newborn neurons.	Radial glial defects in ciliopathy models impair scaffolding and neuron migration, contributing to cortical disorganization [9,26,27,41].
Regional identity	The specification of brain regions along anatomical axes, determining the positional identity of developing neurons.	Ciliopathy-associated gene mutations often cause mispatterning along spatial axes, leading to region-specific malformations [9-11].
Neuroepithelium	A pseudostratified epithelial layer of proliferating neural progenitors forming the early brain tube.	Ciliary signaling defects impair neuroepithelial structure and polarity, leading to disorganized tissue morphogenesis [9-11].
Lumen formation	The creation of hollow, fluid-filled spaces in the neuroepithelium, a hallmark of organized progenitor zone architecture.	Abnormal lumen formation is observed in organoid models of ciliopathy, signaling early disruptions in apicobasal polarity [9-11].
Cortical plate	A postmitotic region where newly generated neurons accumulate and begin to form layered cortical structures.	Many ciliopathies feature disrupted layering of the cortex due to impaired progenitor dynamics and ciliary signaling [10,13,31].
Dorsoventral patterning	Patterning along the dorsal (top) to ventral (bottom) axis, influencing the development of distinct progenitor domains.	Ciliary defects can shift dorsal-ventral signaling balance (e.g., SHH pathway), leading to expansion of inappropriate cell types [2,23].
Rostrocaudal patterning	Patterning along the anterior (rostral) to posterior (caudal) axis, determining spatial identity of brain regions.	Altered rostrocaudal patterning, as seen in RPGRIP1L organoids, results in misexpression of hindbrain markers in forebrain regions [15].

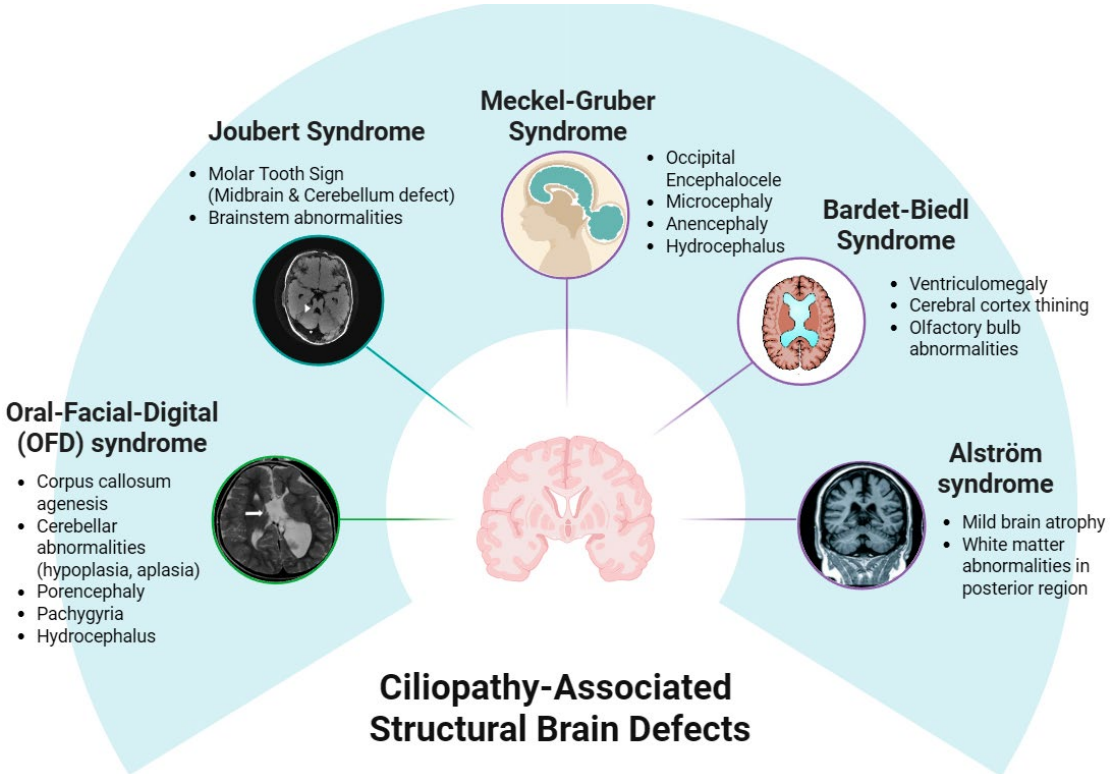

Fig. 1. Representative structural brain abnormalities observed in major human ciliopathies. Orofaciodigital, Joubert, Meckel-Gruber, Bardet-Biedl, and Alström syndromes each display distinct neuroanatomical defects, including callosal agenesis, midbrain and cerebellar malformations, and ventriculomegaly, resulting from early disruptions in cilia-mediated brain development. These structural phenotypes underscore the essential role of primary cilia in human brain morphogenesis.

Despite their small size, they play an essential role in regulating neurodevelopmental signaling pathways, including Sonic Hedgehog (Shh), Wnt, and PDGF, that coordinate spatial patterning and morphogenesis of the embryonic brain [2,23-25]. In particular, primary cilia are enriched on neuroepithelial cells lining the ventricular zone, where they orchestrate neural progenitor proliferation, apical-basal polarity, and cell fate specification [9,26,27]. These processes are vital for forming key anatomical structures, including the ventricular system, radial glial scaffold, midline commissures, and the layered organization of the cerebral cortex [9,28,29].

Ciliary dysfunction, caused by mutations in structural or regulatory components of the cilium, leads to a spectrum of disorders known as ciliopathies (Fig. 1) [2]. Neurologically prominent ciliopathies include Joubert syndrome, Meckel-Gruber syndrome, and Bardet-Biedl syndrome, each characterized by distinct and often diagnostically specific neuroanatomical defects [4,7-9,30]. Common abnormalities include cerebellar vermis hypoplasia, enlargement of the lateral ventricles (ventriculomegaly), agenesis or hypoplasia of the corpus callosum, and malformations of midline structures such as the brainstem and diencephalon [10,13]. In some cases, cortical malformations such as polymicrogyria, pachygyria, or lissencephaly are observed, indicating broader disruption of gyral patterning and cortical lamination [13,31]. These phenotypes are summarized in Fig. 1, which illustrates the distinct structural abnormalities observed in major human ciliopathies.

For example, the hallmark "molar tooth sign" seen in Joubert syndrome reflects a triad of cerebellar vermis hypoplasia, a deepened interpeduncular fossa, and thickened, horizontally oriented superior cerebellar peduncles—anatomical features clearly visualized on axial MRI [32]. Meckel-Gruber syndrome, a more severe ciliopathy, frequently presents with occipital encephalocele, markedly dilated ventricles, and cortical thinning, highlighting the cilia's early influence on neural tube closure and ventricular morpho-

genesis [8,13,33]. Bardet-Biedl syndrome, though clinically heterogeneous, may involve thinning of the corpus callosum and mild ventriculomegaly alongside systemic features [34]. These gross and microanatomical hallmarks underscore the central role of primary cilia in orchestrating spatial organization and morphogenetic patterning during early human brain development.

BRAIN ORGANOID MODELS OF CILIOPATHY

Although mouse models deficient in genes such as Tmem67 and Cep290 have significantly advanced our understanding of ciliary function during brain development, they fall short of capturing the full anatomical complexity of human ciliopathies [16,35-38]. Key interspecies differences, such as the lack of cortical gyrification, oversimplified ventricular architecture, and accelerated neurogenic timelines limit their capacity to model human-specific morphogenetic processes. For instance, while Rpgrip1l-mutant mice display pronounced disorganization of the ventral diencephalon, hypothalamus, and spinal cord, such anomalies have not been reported in human ciliopathy patients [14,17], highlighting model-specific divergence. Furthermore, core features like axon guidance defects, well documented in Joubert syndrome, are notably absent in corresponding mouse models, reinforcing the anatomical and physiological disconnect between animal systems and human pathology [18,19].

To overcome these limitations, brain organoids derived from human pluripotent stem cells have emerged as spatially and anatomically informative in vitro models of early corticogenesis. These systems self-organize into structures resembling ventricular zones, subventricular compartments, and early cortical plates, complete with radial glial scaffolds and apical polarity [39-41]. Importantly, they allow visualization of tissue-level changes, enabling researchers to examine how disruptions in ciliary function affect the formation, maintenance, and patterning of neuroepithelial structures.

Recent studies have utilized CRISPR engineered human iPSC derived brain organoids to model ciliopathy associated genes, including RPGRIP1L [15], INPP5E [42], and ARL13B [43], revealing phenotypes that closely reflect human pathology while addressing the limitations of traditional animal models. Fig. 2 illustrates the overall organoid modeling strategy discussed in this section, from CRISPR-mediated gene editing to phenotype-based characterization of ciliopathy models, including representative outcomes such as altered SHH signaling and regional patterning defects. For example, RPGRIP1L-deficient spinal cord organoids maintain ventral neural tube specification, including expression of OLIG2-positive progenitors and ISL1/2-positive motor neurons. However, they exhibit a human-specific defect in anterior-posterior patterning, with ectopic induction of cervical and hindbrain motor neuron markers such as PHOX2B and TBX20. This phenotype arises early in development, following reduced cilia density and downregulation of axial identity genes such as CDX2 and posterior HOX genes. Despite preserved ciliary morphology, key membrane proteins like ARL13B and ADCY3 are diminished, suggesting impaired ciliary gating. These findings indicate that RPGRIP1L maintains regional identity through early control of ciliary composition and patterning cues [15].

Similarly, cortical organoids carrying the INPP5E D477N mutation exhibit hallmark ciliopathy features driven by disrupted phosphoinositide metabolism and dysregulated ciliary signaling [42]. Although the overall ciliary architecture remains preserved, loss of INPP5E's 5-phosphatase activity leads to pathological accumulation of $PI(4,5)P_2$ within the ciliary membrane. This causes abnormal retention of negative SHH regulators such as TULP3 and GPR161, resulting in constitutive SHH pathway activation, reflected by increased GLI1 and PTCH1 expression and decreased GLI3 repressor levels. These changes drive a shift toward ventral cortical identity, with loss of dorsal markers (PAX6, EMX1, TBR2, CTIP2) and upregulation of ventral markers including GSX2, DLX2, NKX2.1, COUPTFII, and ISL1/2. The phenotype is reversible by SHH inhibition, confirming that INPP5E normally acts as a suppressor of SHH activation during forebrain development.

Likewise, telencephalic organoids lacking ARL13B exhibit ventral forebrain expansion through a distinct mechanism involving ciliary membrane disruption and enhanced SHH pathway activation [43]. ARL13B knockout leads to fewer and shorter cilia with defective membrane compartmentalization. GPR161 fails to localize properly to the cilium, removing its inhibitory influence on SHH signaling. Consequently, SHH signaling is enhanced even in the absence of exogenous ligand, leading to strong induction of ventral markers such as NKX2.2. These results suggest that ARL13B controls SHH sensitivity by regulating the membrane environment of the cilium, and that its loss results

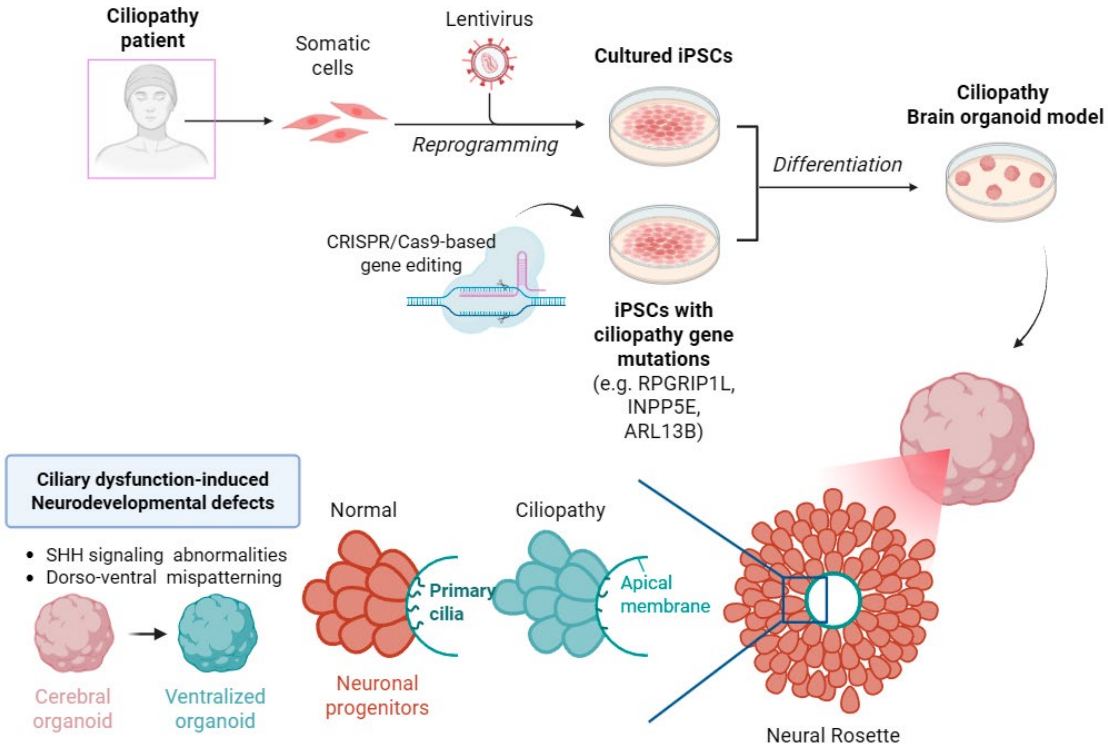

Fig. 2. Schematic overview of brain organoid modeling for ciliopathy. Patient-derived or CRISPR-edited iPSCs are differentiated into brain organoids to study the consequences of primary cilia dysfunction. Ciliary gene mutations, such as INPP5E or ARL13B, result in apical polarity loss, disrupted neuroepithelial organization, and region-specific patterning defects such as cortical ventralization.

in unrestrained ventral fate commitment during cortical development. Other key ciliopathy-associated genes such as TMEM67 and CEP290 have been extensively studied in animal models and are known to play critical roles in brain development. However, organoid-based modeling of these genes remains scarce, and robust phenotypic validation using human brain organoids is still lacking. Future studies employing CRISPR-based perturbation of these genes in organoid systems may further elucidate their roles in human-specific neurodevelopmental contexts.

Taken together, these studies highlight the strength of brain organoids as anatomically meaningful models for exploring how ciliary dysfunction alters human brain patterning. Although RPGRIP1L, INPP5E, and ARL13B affect different molecular pathways, their disruption leads to regional identity shifts and spatial mispatterning through altered ciliary signaling. Unlike traditional animal models, brain organoids preserve early neuroepithelial architecture, such as apical polarity, lumen formation, and layered progenitor zones, allowing for direct analysis of structural and molecular abnormalities. From an anatomical perspective, organoids enable the study of human-specific morphogenesis in three dimensions. As organoid technology advances, these models are expected to become essential tools not only for elucidating disease mechanisms in ciliopathies but also for guiding anatomically informed therapeutic strategies.

PERSPECTIVES AND FUTURE DIRECTIONS IN ORGANOID-BASED MODELING OF CILIOPATHY

Brain organoids have emerged as transformative tools in the study of human neurodevelopmental disorders with anatomical specificity, particularly in the context of ciliopathies. By faithfully recapitulating early tissue organization, such as neuroepithelial polarity, lumen formation, and regional patterning, organoids enable anatomically grounded analyses of how ciliary dysfunction disrupts morphogenetic processes in the human brain.

Despite their clear advantages over traditional models, current brain organoid systems still face limitations. Many

protocols generate immature tissues with limited long-range connectivity, restricted laminar complexity, and no true cortical folding, which constrain their application to later developmental stages [44-46]. In the context of ciliopathies, where anatomical hallmarks often emerge early, organoids provide valuable insight into early-stage pathogenesis but may not fully recapitulate long-term consequences such as cerebellar circuitry development or white matter tract formation [47].

Nonetheless, recent methodological advances continue to improve the structural fidelity and reproducibility of brain organoids. Innovations such as microwell-based aggregation systems [48], bioengineered scaffolds [49], and guided patterning approaches enhance size control and axial organization [50], allowing for more consistent modeling of disease-relevant anatomical features. Integration with high-resolution imaging, spatial transcriptomics, and live-cell lineage tracing further expands the resolution at which organoid-derived phenotypes can be interpreted.

Looking forward, brain organoid platforms hold strong potential not only as investigative tools but also as translational models for therapeutic development in ciliopathies. Patient-derived organoids allow for personalized phenotyping of structural and signaling defects, enabling the identification of mutation-specific vulnerabilities. Recent studies have demonstrated the feasibility of using CRISPR-based gene correction in organoids to reverse early neurodevelopmental defects, providing proof-of-concept for potential gene therapy applications [51]. In addition, brain organoids can be employed in high-throughput drug screening pipelines to identify small molecules that modulate ciliary signaling, which may correct downstream patterning abnormalities [48]. Integration with bioengineered systems, including microfluidic platforms and regionally fused assembloids, further enhances the physiological relevance of these models and supports their future use in preclinical testing [52,53].

From an anatomical perspective, brain organoids are not merely in vitro derivatives of human cells, but structurally self-organizing systems that reconstitute key aspects of early brain morphogenesis. In modeling ciliopathy, they uniquely enable spatial dissection of how single-gene defects alter regional identity, progenitor architecture, and patterning dynamics. As technologies mature, brain organoids will likely become indispensable platforms for uncovering the structural basis of human congenital brain disorders and for anatomically guided translational research.

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