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Experimental models of human cortical malformations: from mammals to 'acortical' zebrafish

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ABSTRACT

Human neocortex controls and integrates cognition, emotions, perception and complex behaviors. Aberrant cortical development can be triggered by multiple genetic and environmental factors, causing cortical malformations. Animal models, especially rodents, are a valuable tool to probe molecular and physiological mechanisms of cortical malformations. Complementing rodent studies, the zebrafish (*Danio rerio*) is an important model organism in biomedicine. Although the zebrafish (like other fishes) lacks neocortex, here we argue that this species can still be used to model various aspects and brain phenomena related to human cortical malformations. We also discuss novel perspectives in this field, covering both advantages and limitations of using mammalian and zebrafish models in cortical malformation research. Summarizing mounting evidence, we also highlight the importance of translationally-relevant insights into the pathogenesis of cortical malformations from animal models, and discuss future strategies of research in the field.

1. Introduction

Mammalian neocortex regulates higher mental functions, including general movements, cognition, perception, and complex behaviors (Jawabri and Sharma, 2022; Molnar et al., 2019). It also modulates the autonomic nervous system to control various key physiological (e.g., cardiovascular, gastrointestinal and respiratory) processes (Mizuno-Matsumoto et al., 2020). Emerging during embryonic development, neocortex is organized in six cortical layers, including include molecular (I), external granular (II), external pyramidal (III), internal granular (IV), internal pyramidal (V) and multiform (VI) layers (El-Drieny et al., 2015). Functional of units of mammalian cortex are represented by microcolumns - large vertical neuronal groups that overlap with each other and modulate complex brain processes (Arai and Taverna, 2017; Kelava and Lancaster, 2016; Narayanan et al., 2017). Cortical development requires normal functioning of multiple common (evolutionarily conserved) brain genes, whose genetic deficits cause cortical malformations (Tables 1 and 2). However, cortical malformations are multifaceted in nature, and in addition to genetic causes, are also induced by environmental factors during cortical development, strongly affecting neuronal proliferation, differentiation, migration and organization (Barkovich et al., 2012; Barkovich et al., 1996; Guerrini and Dobyns, 2014).

Cortical malformations are a diverse family of rare brain disorders that result from aberrant neurodevelopment. For example, cortical dysplasia is often caused by kinesin family member 2 A (*KIF2A*) gene mutations (Kalantari and Filges, 2020). Other common cortical malformations include focal cortical dysplasia (FCD), lissencephaly and polymicrogyria (PMG, Table 1). Clinical FCD is characterized by developmental delay (Wang et al., 2020), cognitive deficits (Allone

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Table 1
Selected examples of major clinical symptoms of human cortical malformations.

Neurological	Neuromorphological	Other	References
Focal cortical dysplasia			
Epilepsy, focal neurological deficits, cognitive deficits, developmental delay, motor dysfunctions, behavioral disturbances and autism	Abnormal cortical layering with radial microcolumns, heterotopic neurons in the white matter, hypertrophic neurons, neurons with abnormal dendrites, cytomegalic and dysmorphic neurons, cortical tubers and reactive astrocytes		(Crino, 2015; Tahta and Turgut, 2020)
Lissencephaly			
Epilepsy, cognitive deficts, intellectual disability, motor dysfunctions, behavioral disturbances and autism	Agyria (absence of convolutions), pachygyria (thick convolutions), subcortical band heterotopia, cerebellar vermis hypoplasia and microcephaly		(Di Donato et al., 2017; Kolbjer et al., 2021)
Polymicrogyria			
Epilepsy, delayed motor and language development, spastic paresis, pyramidal and cerebellar signs, facio-pharyngoglosso-masticatory paresis, restricted tongue movements, drooling and sensorineural hearing loss	Multiple small gyri with abnormal cortical layering, bilateral white matter abnormalities, brainstem and cerebellum atrophy	Esotropia, feeding problems, arthrogryposis, club feet, micrognathia, low-set ears, macrostomia and hypothyroidism	(Jansen and Andermann, 2005b; Teixeira et al., 2007; Wang et al., 2016)

et al., 2020), infantile spasms (Kang et al., 2013) and epilepsy (Sisodiya, 2004). FCD occurs during cell proliferation and differentiation stages of the fetal brain development, thereby disrupting cortical lamination and cells morphology, as well as causing infantile spasms and intractable epilepsy (Iffland et al., 2019; Wong and Roper, 2016).

Genetic causes of FCD include mutations in genes of the mammalian target of rapamycin (mTOR) signaling pathway (Iffland et al., 2019; Scheffer et al., 2014; Sim et al., 2016) (Table 2), such as the mTOR pathway activator genes (*AKT3, MTOR, PIK3CA, RHEB*) and germline loss-of-function mutations of genes of mTOR inhibitors (*DEPDC5, NPRL2, NPRL3, TSC1* and *TSC2*) (Scheffer et al., 2014; Sim et al., 2016; Weckhuysen et al., 2016). For instance, FCD is linked to the hyper-activated mTORC1 (Baybis et al., 2004), which plays an important role in synaptic plasticity, learning and memory (Hoeffer and Klann, 2010). FCD also shares overlapping phenotypes associated with upregulated phosphatidylinositol-3-kinase (PI3K)/AKT/mTOR pathway (Jansen et al., 2015), critical for maintaining the balance between anabolic and catabolic metabolism and controlling various cellular processes, such as growth, proliferation, differentiation and survival (Laplante and Sabatini, 2012). The AKT complex regulates cell signaling in response to insulin and growth factors, and is involved in multiple biological processes including cell proliferation, differentiation, apoptosis, tumorigenesis, glycogen synthesis and glucose uptake (Alcantara et al., 2017). Moreover, *RHEB* mutation elevates ribosomal protein S6 phosphorylation, indicating mTOR activation in the region of the brain lesion, and linking brain somatic *RHEB* mutations to FCD (Zhao et al., 2019).

Furthermore, germline and 2-hit brain somatic variants in the

Table 2
Main genes associated with cortical malformations clinically and the presence of their relevant genetic models in different animal models.

Genes	Biological role in humans related to brain malformations	Non-human primates	Rodents	Zebrafish
Focal cortical dysplasia				
DEPDC5	Inactivates mTOR signaling	+	+	+
NPRL3	Inactivates mTOR signaling	+	+	+
NPRL2	Enhances mTOR signaling	+	+	+
MTOR	Enhances mTOR signaling	+	+	+
PIK3CA	Enhances mTOR signaling	+	+	+
TSC1	Inactivates mTOR signaling	+	+	+ (*a, b*)*
TSC2	Inactivates mTOR signaling	+	+	+
PTEN	Regulates brain development during cell proliferation and differentiation, migration, neurite outgrowth, synaptogenesis, and myelination	+	+	+ (*a, b*)*
RHEB	Enhances mTOR signaling	+	+	+
AKT3	Enhances mTOR signaling	+	+	+ (*a, b*)*
Lissencephaly				
*PAFAH1B1***	Positively regulates the activity of the minus-end directed microtubule (MT) motor protein dynein	+	+	+ (*a, b*)*
DCX	MT-associated protein required for neuronal migration and cortex lamination	+	+	None
TUBA1A	Major constituent of MT involved in process related to cell division	+	+	+
YWHAE	Adapter protein implicated in the regulation of various general and specialized signaling pathways	+	+	+ (*a, b*)*
ARX	Critical for maintenance of specific neuronal subtypes in the cerebral cortex and axonal guidance in the floor plate	+	+	+ (*a, b*)*
TUBG1	Major constituent of MT	+	+	+
RELN	Plays a role in neuronal migration and cortical lamination during embryonic development	+	+	+
Polymicrogyria				
AKT3	Positive regulator of mTOR signaling	+	+	+ (*a, b*)*
CCND2	Positive regulation of cell population proliferation	none	+	+ (*a, b*)*
PAX6	Plays a role in the cerebral cortex regionalization. Negative regulator of neural precursor cell proliferation	+	+	+ (*a, b*)*
TUBA8	Constituent of MT involved in embryonic brain development	+	+	none
TUBB2B	Constituent of MT involved in embryonic brain development	+	+	+
TUBB	Constituent of MT involved in embryonic brain development	+	*Tubb5*	*tubb5*
TUBB3	Constituent of MT involved in embryonic brain development	+	+	none

(*continued on next page*)

Table 2 (*continued*)

Genes	Biological role in humans related to brain malformations	Non-human primates	Rodents	Zebrafish
TUBA1A	Constituent of MT involved in embryonic brain development	+	+	+ (*a, b*)*
WDR62	Plays a role in neuronal proliferation and migration	+	+	+
PIK3R2	Regulates cell growth signaling pathways	+	+	+
PIK3CA	Regulates cell growth and proliferation	+	+	+
NEDD4L	Controls intracellular Na^+-mediated activity of voltage-gated sodium channels in primary cortical neurons	+	+	+
COL4A1	Provides instructions for making one component of type IV collagen	+	+	+
COL4A2	A major structural component of the basement membrane	+	+	+
GPSM2	Orients the mitotic spindle during cell division, is essential for maintaining cell polarity and cell cycle regulation	+	+	+
GRIN2B	Encodes the NR2 subunit of glutamate NMDA*** receptors, an activity-dependent increase in synaptic transmission	+	+	+
WDR62	Plays a role in spindle pole organization and orientation, is involved in brain development during embryonic neurogenesis	+	+	+
ACTG1	Regulates intervertebral disc degeneration via the NF-kappaB-p65 and Akt pathways	+	+	bact2
FH	Regulates fumarase that participates in the Krebs cycle	+	+	+

* The gene has two isoforms, *a* and *b*
** Also known as *Lis1*
*** NMDA - N-methyl-D-aspartate receptor

DEPDC5 gene (which plays a critical role in cellular growth and proliferation and in aspects of neuronal development), a negative regulator of the mTOR pathway, are increasingly recognized in patients with FCD (Jesus-Ribeiro et al., 2021). The NPRL2 protein is expressed in various regions of the human brain, including the frontal, temporal, parietal, and occipital lobes, similar to DEPDC5, and is associated with FCD and intellectual disability (Zhang et al., 2022). Mutations in *NPRL3*, a component of the GATOR1 complex within the mTOR pathway, are associated with epilepsy and cortical maldevelopment (Iffland et al., 2022). Similarly, germline *TSC1/TSC2* gene mutations result in systemic hyperactivation of the mTOR pathway causing abnormal cell growth and proliferation of multiple organ systems, including brain (Jha et al., 2022). Individuals with *PTEN* (phosphate and tensin homologue) gene mutations also typically present cortical malformations (Elia et al., 2012).

Unlike FCD (arising due to cell proliferation and differentiation), lissencephaly occurs during neuronal migration, triggering a severe malformation with undeveloped or even missing gyri and sulci (Fry et al., 2014; Kato and Dobyns, 2003; Wong and Roper, 2016; Wynshaw-Boris et al., 2010). Clinical lissencephaly is characterized by epilepsy, intellectual disability, as well as cognitive, motor, behavioral and social deficits (Table 1). Lissencephaly is mainly caused by mutations in two genes, *PAFAH1B* (Cardoso et al., 2003) and *DCX* (Jang et al., 2013), albeit other genes (e.g., *YWHAE, TUBA1A, TUBG1, RELN)* may also be involved (Kumar et al., 2010; Nagamani et al., 2009; Poirier et al., 2007) (Table 2). The *PAFAH1B* gene plays a key role in cell division and migration with cytoplasmic dynein, a minus end-directed motor of cytoplasmic microtubules (Faulkner et al., 2000; Leventer et al., 2001; Sapir et al., 1997). Mutations in *PAFAH1B1* and *YWHAE* are related to the Miller-Dieker syndrome (MDS), a severe lissencephaly subtype with structural facial abnormalities (Cardoso et al., 2003; Dobyns et al., 1991; Nagamani et al., 2009). While *PAFAH1B1* deletion causes lissencephaly, mutant *YWHAE* is responsible for the structural abnormalities associated with MDS (Nagamani et al., 2009; Schiff et al., 2010).

Mutations in *PAFAH1B* are also associated with isolated lissencephaly sequence (ILS), a mild form of lissencephaly without other structural abnormalities (Fry et al., 2014). Although ILS does not produce any structural abnormalities, both MDS and ILS cause a significant developmental delay and intellectual disability (Cardoso et al., 2003; Dobyns et al., 1991; Fry et al., 2014). Similar to *PAFAH1B1, DCX* also encodes a microtubule-associated protein, regulating microtubular stability and signaling during migration (Subramanian et al., 2019; Tanaka et al., 2004). Since *DCX* is an X-linked gene, its mutations result in complete lissencephaly in men and subcortical band heterotopia (SBH) in women, with mild learning difficulties and epilepsy (Pilz et al., 1998). In addition, heterozygous missense variants in the *TUBG1* gene have been associated with malformations of human cortical development (e.g., lissencephaly), which further result in intellectual disability, developmental retardation and epilepsy (Shen et al., 2021). Similarly, mutations in the *RELN* gene cause a lissencephaly with cerebellar hypoplasia (Chang et al., 2007).

Cortical disorganization followed by neuronal migration triggers PMG, the excessive formation of small gyri (Barkovich, 2010; Golden and Harding, 2010; Judkins et al., 2011). Clinical PMG is characterized by epilepsy, delayed motor and language development, spastic paresis, pyramidal and cerebellar signs, facio-pharyngoglosso-masticatory paresis, restricted tongue movements, drooling and sensorineural hearing loss (Table 1) (Jansen and Andermann, 2005b; Teixeira et al., 2007; Wang et al., 2016). Individuals with PMG are also reported in several congenital anomaly syndromes (Bingham et al., 1998; Dobyns et al., 2008; Jansen and Andermann, 2005a). PMG pathogenesis is complex and heterogeneous, affecting specific cortical zones (single gyrus, portion of one hemisphere, bilateral and asymmetrical, bilateral and symmetrical, or diffused) due to genetic mutations (Table 2), metabolic disorders and viral infections (Harding and Baumer, 1988; Teissier et al., 2014).

For PMG, the most common causative genetic mutations include *TUBA1A* and *PIK3R2*, although other causative genes (*PIK3CA, NEDD4L, COL4A1, COL4A2, GPSM2, GRIN2B, WDR62, TUBB3, TUBB2B, ACTG1* and *FH*) are also involved (Stutterd et al., 2021). For instance, mutations of genes within the PI3K-AKT-mTOR pathway often cause PMG (Alcantara et al., 2017; Nellist et al., 2015). Cyclin D2 (CCND2) is a critical cell cycle regulator and key member of the cyclin D2-CDK4 (DC) complex linked to PMG and other severe cortical malformations (Pirozzi et al., 2021). *PAX6* is a highly conserved developmentally regulated gene on 11p13 (encoding for a transcription factor) and a candidate gene for PMG (Mitchell et al., 2003). Complex cortical malformations associated with mutations in tubulin genes are commonly referred to as tubulinopathies, and involve TUBA1A, TUBB2B and TUBB3 genes (Fallet-Bianco et al., 2014). In addition, mutant variant of the alpha-tubulin TUBA8 gene is also associated with PMG (Abdollahi et al., 2009).

Recognizing the importance of translational cortical malformation research, here we discuss current animal models of these disorders and discuss the existing challenges in this field. For example, although fish lack neocortex, here we argue that these aquatic species can still be used to model various aspects and brain phenomena relevant to human

cortical malformations. We also discuss novel perspectives in this field, covering both advantages and limitations of using mammalian and fish models in cortical malformation research. Summarizing mounting evidence, we also highlight the importance of translationally-relevant insights into the pathogenesis of cortical malformations from animal models, and discuss future strategies of research in the field.

2. Mammalian models of cortical malformations

Various mammalian animal models are an invaluable tool for probing the role of cortex in complex brain functions, its development and pathobiology (Juric-Sekhar and Hevner, 2019; Wong and Roper, 2016; Zhao and Bhattacharyya, 2018). For example, *Depdc5* or *Nprl3* knockout in rodents causes FCD-like cortical deficits (e.g., altered cortical lamination, neuronal dysmorphogenesis, and enhanced neuronal excitability) following the activation of the mTOR pathway (Ishida et al., 2022; Marsan et al., 2016). *Pik3ca* mutant mice (Roy et al., 2015) or mTOR activating mutations have also been studied in this regard (Kassai et al., 2014). For example, *Pik3ca* mutant mice display brain overgrowth (e.g., increased proliferation, cell size and altered white matter) (Roy et al., 2015), whereas selective activation of mTORC1 in mice during embryonic stages induces cortical atrophy with overt apoptosis of neuronal progenitors, associated with upregulation of HIF-1α (Kassai et al., 2014).

In a striking contrast, the activation of the mTORC1 pathway in adulthood resultes in cortical hypertrophy with fatal epileptic seizures (Kassai et al., 2014). Common genetic rodent models of FCD also include knockout of *Pten* (Kwon et al., 2003), *Tsc1* (Meikle et al., 2007) and *Tsc2* (Way et al., 2009). For instance, selective inactivation of *Pten* in postnatal granule neurons of mouse cerebellum and dentate gyrus triggers cell-autonomous hypertrophy, progressive macrocephaly, seizures, and premature death (Kwon et al., 2003). Moreover, *Tsc1* mutant mice display several neurological abnormalities, including enlarged or dysplastic cortical and hippocampal neurons (Meikle et al., 2007), whereas *Tsc2* mutant mice develop post-natal megalencephaly (Way et al., 2009). Intraventricular injection of the high mobility group box protein 1 recombinant (rHMGB1; a ubiquitous nuclear protein released by glia and neurons) mimics human FCD (Yang et al., 2021). Likewise, an exposure of rat embryos to external radiation at 200 cGy produces permanent FCD-like cortical abnormalities (e.g., thinning of the cortical mantle, loss of lamination of the neocortex) accompanied by learning and memory deficits (Cowen and Geller, 1960; Zhou et al., 2011).

Because rodent cortex is naturally lissencephalic, accurate mimicking of this particular cortical pathology in rodents is problematic. Nonetheless, rodents can still be useful for studying cellular and molecular mechanisms of lissencephaly. For example, mutations in *pafah1b1*(also known as *lis1*) in mice contribute to cerebellar granule neuronal migration defects, similar to clinical lissencephaly (Tanaka et al., 2004). Mice with *pafah1b1* mutation exhibit disorganized cortical layers, hippocampus, cerebellum and olfactory bulbs due to lissencephaly-like neuronal migration defects (Wynshaw-Boris et al., 2010). Similar to *pafah1b1* mutants, heterozygous *Dcx* mutant mice also show disrupted lamination in the hippocampus, especially in the CA3 region (Corbo et al., 2002). *Ndel1* mutant mice also present a disorganization of cortical layer formation and hippocampal defects (Youn et al., 2009).

Furthermore, X-linked lissencephaly with abnormal genitalia (XLAG) and developmental epileptic encephalopathy-1 (DEE1) are caused by mutations in the Aristaless-related homeobox (*ARX*) gene, which encodes a transcription factor responsible for brain development (Drongitis et al., 2022). *Arx* knockout (*ArxKO/Y*) and knock-in polyalanine (*Arx(GCG)7/Y*) mice represent genetic models for XLAG and DEE1, and abnormal alternative splicing repertoires in *Neurexin-1* (a gene encoding multiple pre-synaptic organizers implicated in synaptic remodeling) are detected in Arx/alr-1(KO) animals and in Arx(GCG)7/Y mouse epileptogenic brain areas (Drongitis et al., 2022).

Unlike rodents, nonhuman primates present well-developed gyri and sulci, enabling a more accurate recapitulation of lissencephaly. For instance, rhesus monkey fetuses infected with cytomegalovirus early in the second trimester, develop similar lissencephaly to that in congenitally infected humans (Tarantal et al., 1998). Likewise, Brazilian strain of Zika virus infecting female rhesus monkeys in early pregnancy triggers human-like fetal neuropathologies, including lissencephaly (Martinot et al., 2018; Seelke et al., 2020).

As with experimental lissencephaly models, mammals with mutations in PMG-related genes (e.g., *tubb2b*) typically display abnormal cortical development (Jaglin et al., 2009; Stottmann et al., 2013). Moreover, *Gpr56* (family of adhesion G-protein-coupled receptor gene) knockout mice mimic clinical bilateral frontoparietal PMG, forming gyri unusual for normal rodent brain (Li et al., 2008). Similar to those observed in humans, histopathologic features of rhesus monkey fetus infected by cytomegalovirus early in the second trimester of pregnancy reveals PMG (Tarantal et al., 1998). Finally, while cortical malformations are commonly associated with seizures in nearly 75% of patients (Represa, 2019), multiple well-established animal models of epilepsy represent a powerful tool to address this aspect of cortical malformations (Wong and Roper, 2016).

In addition to mice and rats, other animal models for studying cortical development include ferrets (Gilardi and Kalebic, 2021), particularly used for studying the development and maturation of sensory processing (White and Fitzpatrick, 2007). The ferret exhibits certain complex features of brain maturation and neuronal processing that enables targeting cortical malformations. For instance, this species has been used to mimic cortical dysplasia with impaired neuronal migration into the cortical plate and disordered radial glia, since ferrets treated with antimitotic methylazoxymethanol demonstrate reduced levels of brain lipid-binding protein, a well-established molecular biomarker of radial glia (Poluch and Juliano, 2010). Moreover, an important aspect that can be analyzed in the context of cortical malformations in the ferret models is their gyrification. The gyrification in the developing ferret brain occurs postnatally and is largely complete within 28 postnatal days (Neal et al., 2007). During early development of the ferret brain, sulci remain fixed while the gyri expand within the intersulcal segments, thus making relative sulcal depth an indicator of the degree of cortical maturation (Neal et al., 2007), as well as an evolutionary solution to the outstanding growth of the neocortex and necessity to accommodate additional neurons (Gilardi and Kalebic, 2021).

In general, although rodent brain is 1,000-fold smaller than brain in humans (Herculano-Houzel et al., 2006), mouse genetic models of cortical malformations suggest evolutionarily conserved general principles of cortical development and its basic architecture (Defelipe, 2011; Wong and Roper, 2016). However, transcription of genes that are associated with neuronal structure and functional regulation varies between the two species (Bakken et al., 2016; Hawrylycz et al., 2015; Zeng et al., 2012), calling for further research and widening a spectrum of potential model organisms. This also raises the question that if 'cortical development' genes are evolutionarily conserved, they may also play a role in CNS development in other model organisms, such as fishes that lack neocortex (Figs. 1 and 2) but do express genes homologous to those implicated in cortical malformations clinically (Table 2).

3. Zebrafish models relevant to studying cortical malformations

Complementing rodent models in studying genetic and pathophysiological mechanisms of cortical malformations (Subramanian et al., 2019), a small freshwater teleost fish, the zebrafish (*Danio rerio*), emerges as an important animal model in translational neuroscience. Compared to traditional rodent models, zebrafish exhibit some clear advantages for basic research, including easily trackable behavioral patterns, homologous neural and endocrine physiology, fully sequenced genome, high genetic homology with mammals, rapid development and

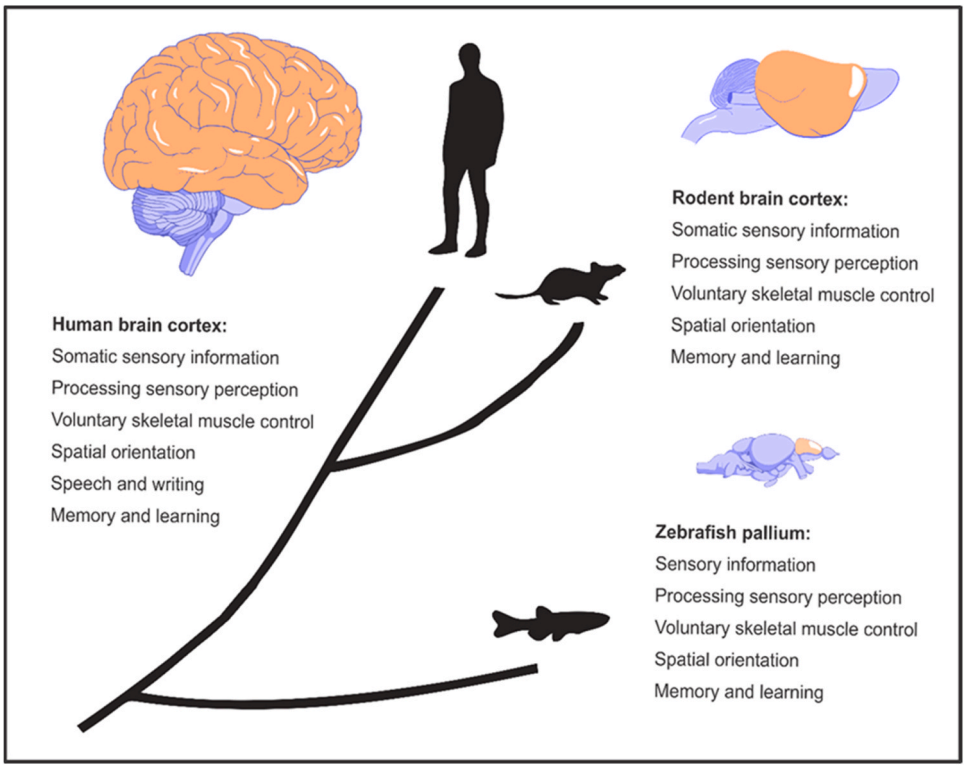

Fig. 1. Comparison of the main functions of human cortex, rodent cortex and zebrafish pallium. Human cortex: peach. Rodent cortex: peach. Zebrafish pallium: light-peach. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

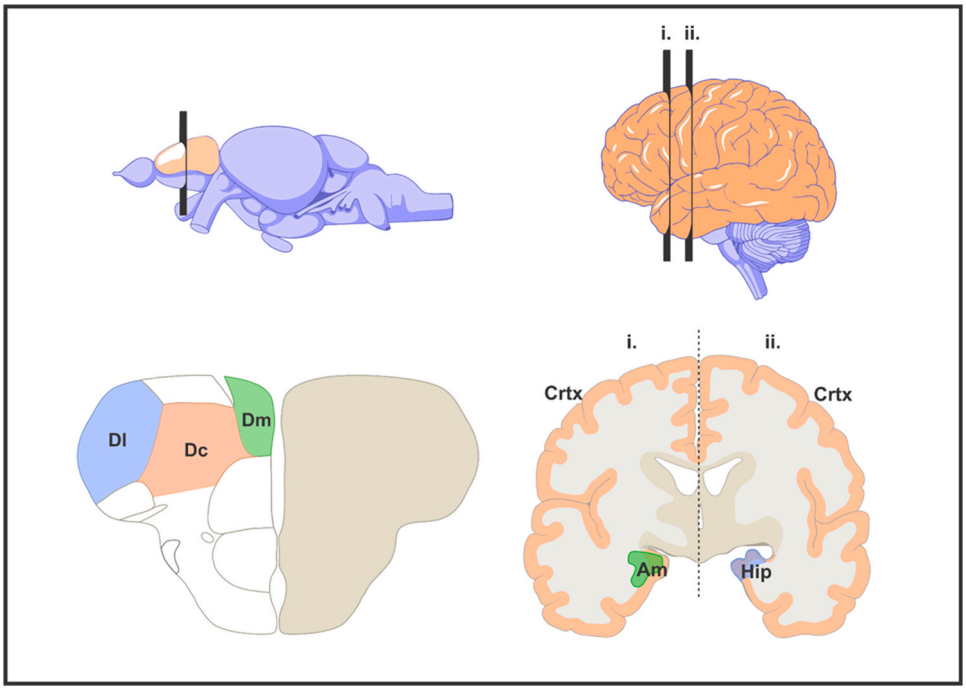

Fig. 2. A brief summary of structural homology between zebrafish pallium and human brain regions. Upper-left: zebrafish brain coronal cut. Bottom-left: zebrafish brain (Dl - blue - dorsal lateral; Dc - peach - dorsal central; Dm - green - dorsal medial). Upper-right: two different sections of human brain coronal cut. Bottom-right: human brain (Hip - blue - hippocampus; Crtx - peach - cortex; Am - green - amygdala). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

high potential for pharmacological (de Abreu et al., 2020; Goldsmith, 2004) and genetic manipulations (Choi et al., 2021; Kalueff et al., 2014; Norton and Bally-Cuif, 2010). Can zebrafish be a reasonably useful model to study various aspects of neuromorphological, genetic and behavioral deficits associated with clinical cortical malformations? On the one hand, the answer to this question is simple: no rum, no fun. In

other words, it is logical to assume that since zebrafish (like other fishes) lack cortex, they in principle cannot model cortical malformations.

On the other hand, this model organism is already so widely used in modeling various aspects of brain functions, and, as will be argued further, may address some aspects of CNS pathogenesis, including its genetic causes and developmental risk factors, hence becoming indirectly relevant to modeling cortical malformations. Furthermore, zebrafish present some additional practical and methodological advantages (compared to rodent), such as external fertilization which simplifies the production of transgenic lines, and the presence of translucent embryos which facilitate probing potential biomarkers of brain malformations (Kimmel, 1989).

Mounting evidence summarized here suggests that zebrafish models can indeed be a useful tool in studying various aspects of cortical malformations. For example, despite their neuroanatomical differences from humans (e.g., acortical brain), zebrafish knockdown of lissencephaly-related genes demonstrates similar retardation in brain development compared to humans (Sun et al., 2009). Likewise, the *TSC2* mutation that induces cortical malformations in mammals, evokes pallium lesions, seizures, anxiogenesis and tyrosine receptor kinase B hyperreactivity in zebrafish (Kedra et al., 2020). Although *depdc5* loss-of-function mutant zebrafish do not show similar pathological traits as mammals with FCD, they do exhibit epileptic activity resembling clinical focal epilepsy (de Calbiac et al., 2021) seen in FCD.

Like rodents, zebrafish can also be used for modeling lissencephaly with abnormal neurodevelopment (Sun et al., 2009). For instance, zebrafish knockdown of *gtdc2* (a lissencephaly-related gene) displays severe movement impairment, hydrocephaly and vision deficits (Manzini et al., 2012). Zebrafish can also be used as an animal model to study PMG and PMG-like retardation in brain development (Ma et al., 2009). Furthermore, zebrafish present functional isoforms of several important genes related to human PMG (e.g., *AKT3, CCND2, PAX6*) (Chen et al., 2011; Kleinjan et al., 2008; Lien et al., 2016) and lissencephaly (*PAFAH1B1, YWHAE, ARX*) (Antón-Galindo et al., 2022; Miura et al., 1997; Sun et al., 2009) (Table 2).

Considering different levels of brain organization, kinesin family member 2 A (*KIF2A*) gene mutations cause most of previously mentioned dramatic cortical malformations, including dysplasia, agyria, and pachygyria accompanied by locomotor deficits in humans (Hatano et al., 2021). While rodent *kif2a* mutants exhibit neurodevelopmental abnormalities and increased seizure susceptibility (Gilet et al., 2020), hippocampal dysfunction (Homma et al., 2018), microcephaly and cortical layer disorganization (Zhang et al., 2019), *kif2a* mutant zebrafish exhibit clinically relevant hypoactivity, working memory deficits, seizure susceptibility and prominent gray matter reduction from telencephalon to hindbrain (Partoens et al., 2021). Despite the viability of these fish mutants, mammalian-like cognitive decline in these fish may be linked to putative 'teleostean hippocampus' located in zebrafish lateral pallium (Mueller et al., 2011). In general, these findings support high homology between memory-related structures of fish and mammals, and also imply that at least short-term memory can be only slightly controlled by neocortex since it is well-represented in naturally acortical zebrafish.

Furthermore, since zebrafish display a well-characterized set of behavioral and electrophysiological phenotypes related to epilepsy, these fish may also be a useful tool for studying intractable epilepsy (Table 1), another key phenotype commonly associated with cortical malformations (Baraban et al., 2005; Cunliffe, 2016; Hong et al., 2016; Winter et al., 2008). At the same time, compared to mammals, zebrafish also show generally high neuroplasticity (Labusch et al., 2020). For example, adult neurogenesis in zebrafish occurs in multiple CNS regions, such as the pallium and the spinal cord (McIntosh et al., 2017; Than-Trong and Bally-Cuif, 2015), enabling further cutting-edge studies of how neurogenesis modulates CNS maldevelopment.

However, animal experimental models also present various limitations for using them to study cortical malformations. For example, rodent models may lack certain human-specific developmental events (e.g., cortical expansion and gyrification) and cell types (e.g., outer radial glia) (Nguyen and Bordey, 2022). Likewise, many mutant mouse and zebrafish models develop rather severe pathological phenotypes and often suffer from premature death (Carson et al., 2012). Moreover, there are fewer mutant or transgenic zebrafish models of brain malformations compared to rodent and human genetic evidence for cortical defects (Nguyen and Bordey, 2022).

Zebrafish models also possess overt limitations in the translatability of their data due to certain differences from humans, such as, anatomy (e.g., lack cortex) and brain development (Parker et al., 2013). Other limitations stem from a crucial role of neurogenic stem cell polarity for mammalian cortex development (Andrews et al., 2022), and a different way of telencephalon formation (by evagination) in teleost fishes (Folgueira et al., 2012). Additionally, the genome duplication event in teleost fishes (Lu et al., 2012) further complicates genetic analyses of CNS malformations in zebrafish, since some related genes may exist in duplicates or be missing (Table 2).

Clearly, multiple other aspects remain poorly understood in regard to modeling cortical malformation in rodents, yet alone in zebrafish (Table 3). For example, there are prominent sex differences in human brain anatomy (e.g., females on average have larger volume at the right frontal pole, insular cortex, the left parahippocampal gyrus and lateral occipital cortex) (Ruigrok et al., 2014) and in disorders associated with cortical malformations (e.g., FCD is more common in boys than girls) (Ortiz-González et al., 2013). While sex differences have been found in zebrafish brain (Zhai et al., 2022) and in behavioral and neuropharmacological responses (Genario et al., 2020), it remains unclear whether zebrafish models of CNS maldevelopment would parallel potential sex differences in human cortical malformations. Furthermore, beyond genetic causes per se, epigenetic factors play an important role in controlling gene expression during complex processes, such as fetal brain development, and the disruption of epigenetic regulation contributes to neurodevelopmental disorders (Lewis et al., 2021). While both rodent and zebrafish models have been developed for studying the role of epigenetics modulations in CNS functions (Balasubramanian et al.,

Table 3
Selected open questions related to zebrafish models of human cortical malformations.

Questions
How important is potential homology between mammalian neocortex and zebrafish central pallium (Fig. 1) in terms of developing models of human cortical malformations?
Does the role of adult neurogenesis in brain recovery of zebrafish mutants parallel its role in mammalian cortical malformations?
Are there significant differences or similarities between mammals with malformed neocortex and healthy naïve zebrafish, considering behavior, neurochemistry and key CNS genes expression?
What compensatory mechanisms support CNS functions in mammals, including those with cortical malformations? Do these potential mechanisms resemble naïve zebrafish CNS functions?
Which zebrafish non-telencephalic brain structures perform functions related to mammalian neocortex? What is the homology between these structures in mammals and fish?
Are there chemical agents evoking behavioral deficits in zebrafish that resemble mammals with cortical malformations?
Are there chemical agents diminishing CNS maldevelopment in zebrafish? Do these drugs impact the risks of cortical malformations in humans?
Are there sex differences in zebrafish models of CNS maldevelopment that would parallel potential sex differences in human cortical malformations?
What gene therapy can be used as a cortical malformations therapy? Can these drugs be screened in vivo using zebrafish models first?
Can cortical malformations promote neurodegeneration in mammals and how can zebrafish be used to study this potential pathogenetic link and its molecular mechanisms?
What are epigenetic correlates of cortical malformations in humans? Do zebrafish models have similar profiles following genetic ablation of their genes orthologous to human genes involved in cortical maldevelopment?

2019; Lakstygal et al., 2018), the role of epigenetic regulation of brain development in fish models remains poorly understood. For example, it is unclear whether gene orthologues of epigenetic correlates of cortical malformations in humans play a similar role in zebrafish neurodevelopment, and whether zebrafish models would have similar profiles of epigenetic regulation (compared to controls) following genetic ablation of critical genes orthologous to human genes involved in cortical maldevelopment.

In conclusion, animal experimental models, including zebrafish, are an important tool to study cortical malformation, as they (despite lacking neocortex) not only possess well-described homologous structures that share main functions in the brain (Figs. 1 and 2), but also express various genes associated with cortical malformations clinically (Table 2) that are shared across all vertebrates. Some of these genes are highly evolutionarily conserved, and their knockout induces aberrant brain development in zebrafish, albeit not conventional cortical malformations per se. The reason why zebrafish may not have some of deficits resembling clinical cortical malformations can be due to the unique everted telencephalon formation in teleost fishes. Nevertheless, some of zebrafish pallial and subpallial areas correspond to some of mammalian neocortical regions, hippocampus, striatal and pallidal structures, as well as amygdala (Fig. 2). Thus, while many questions in this field remain open (Table 3), and despite clear limitations to the degree and fidelity to which animal models may mimic human pathology and physiology, we argue here that zebrafish generate important, translationally-relevant insights into the pathogenesis of cortical malformations, also offering a more throughput, less time-consuming and cheaper complementary drug and genetic bioscreening system, compared to traditional rodent models.

Declaration of Competing Interest

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