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What disorders of cortical development tell us about the cortex: one plus one doesn't always make two

M. Chiara Manzini[1] and **Christopher A. Walsh**[1]

[1] Division of Genetics, Manton Center for Orphan Disease Research and Howard Hughes Medical Institute, Children's Hospital Boston, Boston, MA, 02115

Abstract

The unique size and complexity of the human cerebral cortex are achieved via a long and precisely regulated developmental process controlling neurogenesis, neuronal migration and differentiation. Traditionally, disorders of cortical development have been classified on the basis of the most obvious defects in one of these developmental steps. However, the more we learn about the cellular biological roles of genes that are essential for cortical development, the more we realize that these functions map onto molecular processes, but not so cleanly onto anatomical processes. Essential genes might be involved both in proliferation and migration as well as differentiation, reflecting roles for underlying molecular mechanisms in different phases of development and causing a stunning variety of cortical defects.

Introduction

After cortical neurons are generated from radial glial progenitor cells close to the ventricle, they migrate towards the pial surface using radial glial processes as scaffold and form an ordered laminar structure (Fig. 1A). Malformations of cortical development have been traditionally classified based on which biological process is likely to be affected and grouped under disorders of proliferation, migration and cortical organization [1–3]. In the disorders of proliferation (or of the balance between proliferation and apoptosis), the number of cells is significantly reduced, resulting in an abnormally small head (microcephaly) (reviewed in [4–6]). In the disorders of migration, neurons do not reach their correct destination in the cortical plate, either by remaining at the ventricular surface (periventricular heterotopia), arresting in the white matter (subcortical band heterotopia) or forming a disordered, often thickened, cortical plate. This thicker cortex affects the formation of normal gyration, leading to a simplified gyral pattern (pachygyria) or a smooth appearance of the cortical surface (lissencephaly), sometimes with overmigration of neurons to the pial surface (cobblestone lissencephaly) [3, 7, 8]. The third category, disorders of cortical organization or late migration, comprises mostly the polymicrogyrias, a heterogeneous group of malformations with multiple small gyri and an abnormally thin or thick cortex, sometimes so severely affecting brain structure as to cause clefting between the ventricular and meningeal surface (schizencephaly) [9].

Corresponding author: Walsh, Christopher A. (christopher.walsh@childrens.harvard.edu).

The identification of clear diagnostic criteria to enroll suitable families for genetic analysis has quickened the pace of discovery of genes responsible for many of these diseases as multiple families with the same phenotype could be grouped for linkage studies. The genes associated with each type of disorders often supported the mechanistic hypotheses behind the clinical classification. Almost all microcephaly genes identified to date encode for centrosomal proteins and DNA repair pathway members, whose perturbation is expected to disrupt cell division ([5, 10] for review, and [11–14]). Likewise, genes responsible for lissencephalies and heterotopias are predicted to cause neuronal migration defects, by affecting cytoskeletal stability and trafficking, or by altering responses to extracellular signaling and cellular interactions with the extracellular matrix [7, 8]. Only the polymicrogyrias still defy the identification of a common mechanistic cause and may in fact comprise several different disorders.

As new genes are identified and more diverse patient cohorts are used for resequencing, a more complex picture is emerging shaking the one gene/one mechanism/one malformation hypothesis and sometimes identifying all three malformation categories in the same patient. By combining human genetics analyses with functional studies in animal models we are beginning to understand how cortical malformation genes work together to form the normal and diseased cortex. Here, we will discuss recent advances in the study of cortical malformation genes affecting cytoskeletal function to show how phenotypic heterogeneity can be explained by a single gene affecting multiple stages of differentiation or by different genes converging on the same mechanism.

One gene – one malformation? Clinical variability in cortical malformations

α-dystroglycanopathies, a group of congenital muscular dystrophies associated with brain malformations (also reviewed in this issue), were among the first examples of mutations in the same gene [15] and sometimes the same mutation [16, 17] resulting in a varied spectrum of brain phenotypes ranging from cobblestone lissencephaly or pachygyria to polymicrogyria, to no brain defects at all [18, 19] and blurring the boundary between disorders of neuronal migration and cortical organization.

In the past year, studies on microcephaly cohorts revealed that the border between disorders of proliferation and migration is also not as sharp as previously thought. The very recent identification of the *WDR62* gene as the second most common known genetic cause of microcephaly [11–13], 11 years after the mapping of the genetic locus [20], revealed that the malformations associated with mutations in this gene are extremely variable, including pachygyria, lissencephaly, polymicrogyria, schizencephaly, hippocampal and cerebellar abnormalities. Patients with *WDR62* mutations can even show considerable hemispheric asymmetry in the findings within a given brain [12]. Such clinical heterogeneity contributed to the long delay in the identification of *WDR62*, since many cases would not have been grouped together for linkage studies. However, even *ASPM* mutations, the most common cause of primary microcephaly, have been occasionally associated to variable cortical phenotypes in a large resequencing effort, revealing instances of gyral simplification, polymicrogyria and corpus callosum agenesis [21]. From a clinical genetics standpoint these findings complicate the choice of a specific genetic test for molecular diagnosis, and more resequencing of large patient cohorts with variable malformation patterns may be beneficial to determine the frequency of mutation for each gene and develop better testing guidelines. From the functional standpoint this phenotypic differences support the hypothesis that cortical malformation genes may be involved in multiple developmental steps.

One gene - one function? The centrosome in proliferation and migration

Considering the unique morphology of neurons it should not be surprising that the cytoskeleton is emerging as a key element in the regulation of all aspects of neuronal differentiation. Cytoskeletal components or regulators are mutated in all three categories of cortical malformations (Table 1) and understanding the roles of the cytoskeleton in cortical development can help reconcile how different malformations may be caused by the same gene. Six of the seven genes identified for microcephaly vera (or primary microcephaly, defined as a small brain with normal gyral pattern and few or no other associated features) encode proteins localized in or around the microtubule organizing center (MTOC) in the centrosome (*ASPM*, *CDK5RAP2*, *CENPJ*, *CEP152*, *STIL*, *WDR62*) [5, 11–13]. Since these proteins are expected to regulate the mitotic spindle, the prevailing hypothesis is that mitotic defects in the neuronal progenitors underlie the reduction in neuronal number in the microcephalic brain [5]. In fact, recent studies removing *Cdk5rap2* [22, 23] or *Aspm* [24, 25] in the developing mouse cortex found early cell cycle exit in the progenitor cells leading to early neuronal differentiation and a likely depletion of the progenitor pool (Fig. 1Bi). Similar results were observed by knockdown of pericentrin, a centrosomal protein involved in microcephalic osteodysplastic primordial dwarfism [23]. Questions are still open on the exact mechanisms leading to cell cycle exit, whether the mitotic spindle is abnormal as found in some models [22, 24] but not in others [23, 25], and on the differentiation and survival of the prematurely born neurons. Cortical size reduction in the *Aspm* mice has been modest compared to the human phenotype [22, 25], possibly due to the reduced proliferation potential of murine progenitor responsible for the generation of a much smaller cortex than the human one [26]. The generation of additional mouse models or allelic series involving multiple centrosomal proteins responsible for microcephaly may lead to a more severe phenotype and provide new mechanistic insight into the condition of the mitotic spindle.

The multiple brain malformations identified in microcephaly patients with mutations in *WDR62* and to a lesser extent in *ASPM* argue that the fewer neurons generated may also be impaired in their ability to migrate properly [12, 13, 21], as seen in studies on the lissencephaly gene *LIS1*, which established the importance of the centrosomal function in both neurogenesis and migration. Lis1 is a microtubule stabilizing protein acting primarily at the centrosome [27, 28] and *de novo* dominant mutations or deletion in the *LIS1* gene cause classic lissencephaly [29]. While mice with heterozygous *Lis1* loss of function only show mild lamination defects in the cortex and a delay in neuronal migration [30–32], the combined loss of Lis1 and its binding partners such as the centrosomal proteins Nde1 and Ndel1 and the molecular motor cytoplasmic dynein uncovered how Lis1 acts in multiple developmental processes such as mitotic spindle stability [33, 34], nuclear movement during migration (nucleokinesis) and extension of the leading migratory process [28, 31, 35], and the interaction between the microtubules and the actin cytoskeleton [36]. Microcephaly genes, which are associated with the centrosome and cause multiple cortical malformations, may be involved in a similar array of cellular processes. As a result the cells that survive the primary mitotic defects may not be able to complete neuronal migration due to a secondary disruption in the establishment of cell polarity, nucleokinesis and/or leading process extension (Fig. 1Bii).

One malformation – one mechanism? The microtubules multi-task

The discovery of mutations in *LIS1* and another microtubule-binding protein *DCX* in lissencephaly cases and follow-up studies on the function of these proteins firmly established the importance of microtubule stability in the disorders of cortical migrations (for review see [3, 7]). In the past few years, the structural components of the microtubules themselves, α and β tubulin, have been tied to the pathogenesis of cortical malformations

with different tubulin isotypes causing different malformations and sometime different syndromes altogether: *TUBA1A* in classical lissencephaly [37, 38], *TUBB2B* and *TUBA8* in two different forms of polymicrogyria [39, 40] and *TUBB3* in a wide array of neurological malformations including microlissencephaly, frontal polymicrogyria, gyral simplification or normal cortical appearance all associated with axon guidance defects [41, 42]. These findings suggest that different tubulin isotypes have specific roles in cortical development and tubulin disorders will be reviewed in this issue by Tischfield at al. We will focus on what these genes can tell us about the etiology of polymicrogyria, which mechanistically is the most elusive of the cortical malformations.

Polymicrogyria is a common cortical malformation and is extremely variable in appearance and topography in both imaging and neuropathology studies [9] occasionally accompanying different cortical disorders. The actual cellular mechanisms of this malformation are unclear and recent comprehensive analyses of hundreds of patients with polymicrogyria suggest that it may in fact comprise several different disorders [43, 44]. One possible mechanism for this loss of cortical organization was suggested by studies on the *GPR56* gene, which causes bilateral frontoparietal polymicrogyria (BFPP) in humans [45]. In the *Gpr56* knockout mouse there are regional cortical organization defects where the radial glia orientation is disrupted and the basal lamina is discontinuous, leading to neuronal overmigration to the pial surface [46] (Fig. 1C). These findings are remarkably similar to those observed in both patient neuropathology and animal models of cobblestone lissencephaly, which is often seen in association with α-dystroglycanopathies, and is also characterized by a disruption of the basal lamina, cortical dysplasia and overmigration, primarily due to defects in the radial glial progenitors [47–49], supporting the hypothesis that BFPP and cobblestone lissencephaly may lie on the same spectrum and belong to a common migration disorder caused by radial glial disruption [9, 50].

Unexpectedly, neuropathology studies identified a similar disruption of the radial glial scaffold and neuronal overmigration in a 27-week fetus carrying a dominant missense mutation in *TUBB2B*, which causes asymmetric polymicrogyria of predominantly frontal distribution [39]. Mechanistically, mutations in these genes appear to lead to radial glial instability via different means, loss of interaction with the basal membrane in the case of *Gpr56* [46] and dystroglycan [47], and cytoskeletal destabilization for *TUBB2B* [39, 51]. An analogous phenotype in the mouse is also observed when the meninges are missing due to mutations in the Foxc1 gene [52, 53], suggesting an additional role of structures outside the cortex in regulating its development (also reviewed in this issue).

Together, these findings illustrate how multiple different genetic defects in functionally distinct processes regulating a common structure, the radial glial scaffold, may lead to related anatomical malformations. It will be important to determine whether the radial glia is disrupted in other forms of polymicrogyria, in particular those associated to mutations in *TUBA8* or *TUBB3*, or *WDR62* which also show instances of cobblestone cortex. Other forms of polymicrogyria may have a different origin altogether and only more complete genetic and functional characterizations will help sort through this heterogeneity.

The future

The heterogeneity of clinical presentations of cortical malformations and of the genetic causes of these disorders is staggering, but by organizing the disease genes in functional groups and modeling the genetic lesions and functional interactions in the mouse cortex, we can begin to understand how these genes contribute to normal and abnormal cortical development. As these mechanisms are unraveled, the variability of brain phenotypes becomes less daunting as multiple developmental defects can be explained by different roles

of the same gene or the concerted function of groups of genes. Due to the speed in the identification of novel cortical malformations genes in recent years, several mouse models still need to be generated and crossed with the existing ones. However, due to obvious limitations in the mouse cortex, such as the lack of gyration, more detailed neuropathology and better imaging in human brains are also necessary to instruct or corroborate findings in the mouse.

Multiple genetic causes of cortical malformations are still unknown, particularly as it pertains to polymicrogyria and cobblestone lissencephaly, where extreme genetic and clinical heterogeneity makes linkage studies arduous. Next generation sequencing technologies will surpass the heterogeneity via the sequencing every coding region in the genome or the entire genome of each affected individual and family members (whole-exome or whole-genome sequencing) in order to complete the catalogue of disease mutations. This will help build a framework to start identifying functional groups of genes and separating disorders in different functional categories to illuminate how the cerebral cortex is assembled.

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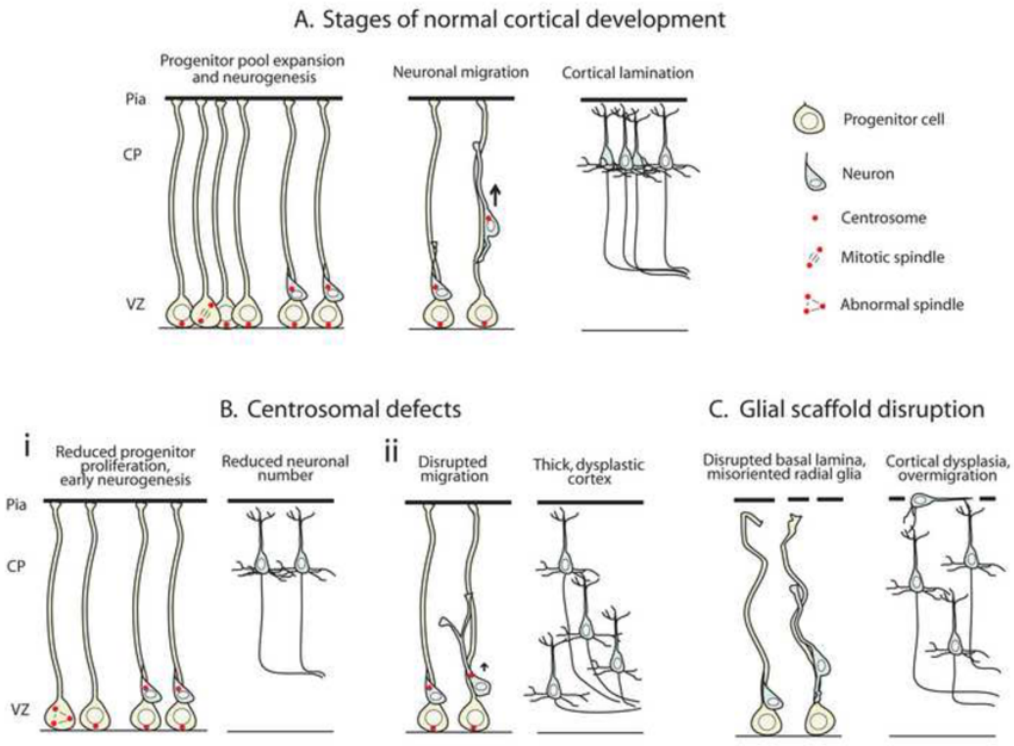

Figure 1. Examples of abnormal cortical development leading to malformations

A. Normal cortical development results from a balance of progenitor cell proliferation, neurogenesis and neuronal migration, leading to normal cortical lamination. Progenitor cells are in yellow and neurons are in blue, for simplicity only one of the cortical layers is shown here. Abbreviations: CP, cortical plate, VZ, ventricular zone. **B.** Centrosomal defects can lead to different malformations: microcephaly (i), where progenitor proliferation is reduced, sometimes due to the formation of abnormal mitotic spindles, and neurogenesis is anticipated; or lissencephaly (ii), where a thickened, disorganized cortical plate is generated following migration defects, reduced cell motility, disrupted leading process formation, uncoupling of the centrosome and nucleus during nucleokinesis. **C.** Disruptions in the orientation of the radial glial scaffold, such as observed in cobblestone lissencephaly and some forms of polymicrogyria, lead to cortical dysplasia and neuronal overmigration through the basal lamina on the pial surface.

Table 1

Gene	Function	Disorder	% cases(# of alleles)	Additional malformations
ASPM	Centrosomal protein	Microcephaly vera	40-55% (86)	Common: simplified gyral pattern/Rare:polymicrogyria, partial agenesis of the corpus callosum, cerebellar hypoplasia
CDK5RAP2	Centrosomal protein	Microcephaly vera	<1% (2)	No cohort studies available
CENPJ	Centrosomal protein	Microcephaly vera	<1% (3)	No cohort studies available
		Seckel syndrome	(1)	
CEP152	Centrosomal protein	Microcephaly vera	<1% (2)	No cohort studies available
STIL	Centrosomal protein	Microcephaly vera	<1% (3)	No cohort studies available
WDR62	Centrosomal protein	Microcephaly vera	5–10% (15)	Common: simplified gyral pattern/Occasional: polymicrogyria, schizencephaly, heterotopias, lissencephaly, corpus callosum hypoplasia, cerebellar hypoplasia, hippocampal dysplasia
PCNT	Centrosomal protein	Microcephalic osteodysplastic dwarfism	100%? (34)	No comprehensive neuroradiology available
LIS1	Microtubule binding	Lissencephaly/SBH	60% (109)	
		Miller-Dieker syndrome	~100% (10)	
DCX	Microtubule binding	Lissencephaly (males)	20–45% (33)	
		SBH (females)	80% (65)	
TUBA1A	Tubulin	Lissencephaly	7% (13)	microcephaly, simplified gyral pattern, subcortical band heterotopia, corpus callosum hypoplasia or agenesis
		LCH	32% (6)	
TUBA8	Tubulin	PMG with optic nerve hypoplasia	(1)	
TUBB2B	Tubulin	Asymmetrical PMG	(5)	
TUBB3	Tubulin	CFEOM +	(28)	microlissencephaly, polymicrogyria, symplified gyral pattern
		Cortical malformations	(6)	
FLNA	Actin binding	PH (females)	~100% (60)	

Abbreviations: CFEOM –congeniral fibrosis of the extraocular muscles, LCH – lissencephaly with cerebellar hypoplasia, PH – periventricular heterotopia, PMG – polymicrogyria, SBH – subcortical band heterotopia.

# of alleles were collected from the Human Gene Mutation Database and the following references: [11, 12, 13, 14, 54]

% of cases with mutations in the gene were collected from the following references: [3, 5, 36]