



ELSEVIER

Available online at www.sciencedirect.com

What disorders of cortical development tell us about the cortex: one plus one does not always make two

M Chiara Manzini and Christopher A Walsh

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 in both 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.

Address

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

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

Current Opinion in Genetics & Development 2011, **21**:1–7

This review comes from a themed issue on
Molecular and genetic bases of disease
Edited by Oscar Marin and Joseph Gleeson

0959-437X/\$ – see front matter
© 2011 Elsevier Ltd. All rights reserved.

DOI [10.1016/j.gde.2011.01.006](https://doi.org/10.1016/j.gde.2011.01.006)

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 (Figure 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 [1,2,3]. 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 [4,5,6]). 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

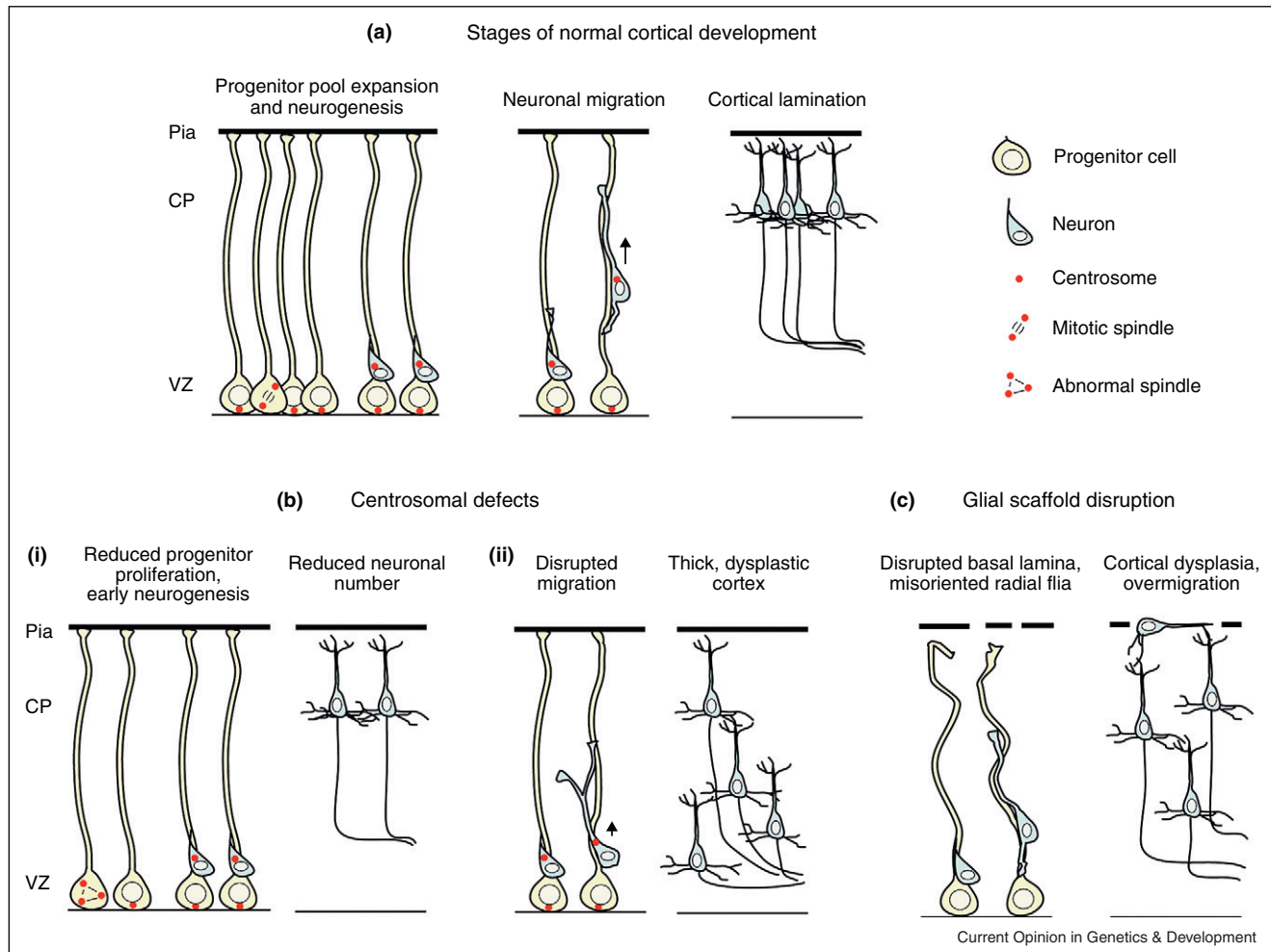
in the white matter (subcortical band heterotopia) or forming a disordered, often thickened, cortical plate. This thicker cortex affects the formation of normal gyration, leading to a simplified gyral pattern (pachygyria) or a smooth appearance of the cortical surface (lissencephaly), sometimes with 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].

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 [11,12,13,14]). 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.

2 Molecular and genetic bases of disease

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.

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^{**},12^{**},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 with 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^{**},12^{**},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

Table 1

Cortical malformation genes encoding cytoskeletal proteins.

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

Abbreviations: CFEOM – congenital 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].

4 Molecular and genetic bases of disease

cortex found early cell cycle exit in the progenitor cells leading to early neuronal differentiation and a likely depletion of the progenitor pool (Figure 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 deletions in the *LIS1* gene cause classic lissencephaly [29]. Although mice with heterozygous *Lis1* loss of function only show mild lamination defects in the cortex and a delay in neuronal migration [30,31^{*},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 (Figure 1bii).

One malformation – one mechanism? The microtubule 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 isoforms 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 isoforms have specific roles in cortical development and tubulin disorders will be reviewed in this issue by Tischfield *et 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^{*}] (Figure 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 [47,48,49^{*}], 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 with 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. Owing to the speed in the identification of novel cortical malformation 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 of 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.

Acknowledgements

We thank Judy Liu, Jill Wildonger, Jenny Yang and Annapurna Poduri for critical reading of the manuscript. M.C.M. is supported by a Development Grant from the Muscular Dystrophy Association and a Hearst Fund Award. C.A.W. is supported by grants from the National Institute of Neurological Disease and Stroke, the National Institute of Mental Health, the Nancy Lurie Marks Family Foundation, the Simons Foundation and the Mantor Center for Orphan Disease Research. C.A.W. is an Investigator of the Howard Hughes Medical Institute.

References and recommended reading

Papers of particular interest published within the period of review have been highlighted as:

- of special interest
- of outstanding interest

1. Mochida GH, Walsh CA: **Genetic basis of developmental malformations of the cerebral cortex.** *Arch Neurol* 2004, **61**:637-640.
2. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB:
 - **A developmental and genetic classification for malformations of cortical development.** *Neurology* 2005, **65**:1873-1887.
 The description and classification of human cortical malformation is detailed in this landmark article.
3. Guerrini R, Parrini E: **Neuronal migration disorders.** *Neurobiol Dis* 2010, **38**:154-166.
4. Kaindl AM, Passemard S, Kumar P, Kraemer N, Issa L, Zwirner A, Gerard B, Verloes A, Mani S, Gressens P: **Many roads lead to primary autosomal recessive microcephaly.** *Prog Neurobiol* 2010, **90**:363-383.
5. Thornton GK, Woods CG: **Primary microcephaly: do all roads lead to Rome?** *Trends Genet* 2009, **25**:501-510.
 - Excellent overview of the functional studies on known primary microcephaly causing genes.
6. Mochida GH: **Genetics and biology of microcephaly and lissencephaly.** *Semin Pediatr Neurol* 2009, **16**:120-126.
7. Kerjan G, Gleeson JG: **Genetic mechanisms underlying abnormal neuronal migration in classical lissencephaly.** *Trends Genet* 2007, **23**:623-630.
 - Excellent overview of the genetic and functional mechanisms of lissencephaly.
8. Francis F, Meyer G, Fallet-Bianco C, Moreno S, Kappeler C, Socorro AC, Tuy FP, Beldjord C, Chelly J: **Human disorders of cortical development: from past to present.** *Eur J Neurosci* 2006, **23**:877-893.
9. Barkovich AJ: **Current concepts of polymicrogyria.** *Neuroradiology* 2010, **52**:479-487.
10. O'Driscoll M, Jeggo PA: **The role of the DNA damage response pathways in brain development and microcephaly: insight from human disorders.** *DNA Repair (Amst)* 2008, **7**:1039-1050.
11. Bilguvar K, Ozturk AK, Louvi A, Kwan KY, Choi M, Tatli B,
 - Yalnizoglu D, Tuysuz B, Caglayan AO, Gokben S *et al.*: **Whole-exome sequencing identifies recessive WDR62 mutations in severe brain malformations.** *Nature* 2010, **467**:207-210.
 With [12**,13**] these are the first instance in which next-generation sequencing has been used to identify cortical malformation gene, revealing the extreme phenotypic heterogeneity of *WDR62* mutations. Whole-exome sequencing was used in this article (i.e. sequencing of every coding exon in the genome).
12. Yu TW, Mochida GH, Tischfield DJ, Sgaier SK, Flores-Sarnat L, Sergi CM, Topcu M, McDonald MT, Barry BJ, Felie JM *et al.*:
 - **Mutations in WDR62, encoding a centrosome-associated protein, cause microcephaly with simplified gyri and abnormal cortical architecture.** *Nat Genet* 2010, **42**:1015-1020.
 With [11**,13**] this article proves the power of next-generation sequencing in identifying previously elusive disease genes. Targeted next-generation sequencing was used here (i.e. sequencing of a large genomic region that could not be tackled using traditional Sanger sequencing).
13. Nicholas AK, Khurshid M, Desir J, Carvalho OP, Cox JJ,
 - Thornton G, Kausar R, Ansar M, Ahmad W, Verloes A *et al.*: **WDR62 is associated with the spindle pole and is mutated in human microcephaly.** *Nat Genet* 2010, **42**:1010-1014.
 With [11**,12**] this article proves the power of next-generation sequencing in identifying previously elusive disease genes. Targeted next-generation sequencing was used here (i.e. sequencing of a large genomic region that could not be tackled using traditional Sanger sequencing).
14. Shen J, Gilmore EC, Marshall CA, Haddadin M, Reynolds JJ, Eyaid W, Bodell A, Barry B, Gleason D, Allen K *et al.*: **Mutations in PNKP cause microcephaly, seizures and defects in DNA repair.** *Nat Genet* 2010, **42**:245-249.

6 Molecular and genetic bases of disease

15. Beltran-Valero de Bernabe D, Voit T, Longman C, Steinbrecher A, Straub V, Yuva Y, Herrmann R, Sperner J, Korenke C, Diesen C *et al.*: **Mutations in the FKRP gene can cause muscle-eye-brain disease and Walker-Warburg syndrome.** *J Med Genet* 2004, **41**:e61.
16. Diesen C, Saarinen A, Pihko H, Rosenlew C, Cormand B, Dobyns WB, Dieguez J, Valanne L, Joensuu T, Lehesjoki AE: **POMGnT1 mutation and phenotypic spectrum in muscle-eye-brain disease.** *J Med Genet* 2004, **41**:115-120.
17. Teber S, Sezer T, Kafali M, Manzini MC, Konuk Yuksek B, Tekin M, Fitoz S, Walsh CA, Deda G: **Severe muscle-eye-brain disease is associated with a homozygous mutation in the POMGnT1 gene.** *Eur J Paediatr Neurol* 2008, **12**:133-136.
18. Clement E, Mercuri E, Godfrey C, Smith J, Robb S, Kinali M, Straub V, Bushby K, Manzur A, Talim B *et al.*: **Brain involvement in muscular dystrophies with defective dystroglycan glycosylation.** *Ann Neurol* 2008, **64**:573-582.
19. Mercuri E, Messina S, Bruno C, Mora M, Pegoraro E, Comi GP, D'Amico A, Aiello C, Biancheri R, Berardinelli A *et al.*: **Congenital muscular dystrophies with defective glycosylation of dystroglycan: a population study.** *Neurology* 2009, **72**:1802-1809.
20. Roberts E, Jackson AP, Carradice AC, Deeble VJ, Mannan J, Rashid Y, Jafri H, McHale DP, Markham AF, Lench NJ, Woods CG: **The second locus for autosomal recessive primary microcephaly (MCPH2) maps to chromosome 19q13.1-13.2.** *Eur J Hum Genet* 1999, **7**:815-820.
21. Passemard S, Titomanlio L, Elmaleh M, Afenjar A, Alessandri JL, Andria G, de Villeneuve TB, Boespflug-Tanguy O, Burglen L, Del Giudice E *et al.*: **Expanding the clinical and neuroradiologic phenotype of primary microcephaly due to ASPM mutations.** *Neurology* 2009, **73**:962-969.
22. Lizarraga SB, Margossian SP, Harris MH, Campagna DR, Han AP, Blevins S, Mudbhary R, Barker JE, Walsh CA, Fleming MD: **Cdk5rap2 regulates centrosome function and chromosome segregation in neuronal progenitors.** *Development* 2010, **137**:1907-1917.
23. Buchman JJ, Tseng HC, Zhou Y, Frank CL, Xie Z, Tsai LH: **Cdk5rap2 interacts with pericentrin to maintain the neural progenitor pool in the developing neocortex.** *Neuron* 2010, **66**:386-402.
24. Fish JL, Kosodo Y, Enard W, Paabo S, Huttner WB: **Aspm specifically maintains symmetric proliferative divisions of neuroepithelial cells.** *Proc Natl Acad Sci USA* 2006, **103**:10438-10443.
25. Pulvers JN, Bryk J, Fish JL, Wilsch-Brauninger M, Arai Y, Schreiber D, Naumann R, Helppi J, Habermann B, Vogt J *et al.*: **Mutations in mouse Aspm (abnormal spindle-like microcephaly associated) cause not only microcephaly but also major defects in the germline.** *Proc Natl Acad Sci USA* 2010, **107**:16595-16600.
26. Kriegstein A, Noctor S, Martinez-Cerdeno V: **Patterns of neural stem and progenitor cell division may underlie evolutionary cortical expansion.** *Nat Rev Neurosci* 2006, **7**:883-890.
27. Feng Y, Olson EC, Stukenberg PT, Flanagan LA, Kirschner MW, Walsh CA: **LIS1 regulates CNS lamination by interacting with mNudE, a central component of the centrosome.** *Neuron* 2000, **28**:665-679.
28. Shu T, Ayala R, Nguyen MD, Xie Z, Gleeson JG, Tsai LH: **Ndel1 operates in a common pathway with LIS1 and cytoplasmic dynein to regulate cortical neuronal positioning.** *Neuron* 2004, **44**:263-277.
29. Dobyns WB, Reiner O, Carrozzo R, Ledbetter DH: **Lissencephaly. A human brain malformation associated with deletion of the LIS1 gene located at chromosome 17p13.** *JAMA* 1993, **270**:2838-2842.
30. Hirotsune S, Fleck MW, Gambello MJ, Bix GJ, Chen A, Clark GD, Ledbetter DH, McBain CJ, Wynshaw-Boris A: **Graded reduction of Pafah1b1 (Lis1) activity results in neuronal migration defects and early embryonic lethality.** *Nat Genet* 1998, **19**:333-339.
31. Youn YH, Pramparo T, Hirotsune S, Wynshaw-Boris A: **Distinct dose-dependent cortical neuronal migration and neurite extension defects in Lis1 and Ndel1 mutant mice.** *J Neurosci* 2009, **29**:15520-15530.
- With reference [34*] this study shows the power of allelic series to unravel functional defects in mouse models of cortical malformations where the murine phenotype is less severe than the human one. In this case loss of the lissencephaly gene Lis1 is combined with the loss of interacting centrosomal protein Ndel1.
32. Gopal PP, Simonet JC, Shapiro W, Golden JA: **Leading process branch instability in Lis1+/- nonradially migrating interneurons.** *Cereb Cortex* 2010, **20**:1497-1505.
33. Feng Y, Walsh CA: **Mitotic spindle regulation by Nde1 controls cerebral cortical size.** *Neuron* 2004, **44**:279-293.
34. Pawlitz AS, Mutch C, Wynshaw-Boris A, Chenn A, Walsh CA, Feng Y: **Lis1-Nde1-dependent neuronal fate control determines cerebral cortical size and lamination.** *Hum Mol Genet* 2008, **17**:2441-2455.
- As in Ref. [32], allelic series of Lis1 with an interacting protein (Nde1 in this case) allows some insight into the functional versatility of this protein, revealing distinct defects in cortical progenitor proliferation and neuronal migration.
35. Tsai JW, Bremner KH, Vallee RB: **Dual subcellular roles for LIS1 and dynein in radial neuronal migration in live brain tissue.** *Nat Neurosci* 2007, **10**:970-979.
36. Kholmanskikh SS, Koeller HB, Wynshaw-Boris A, Gomez T, Letourneau PC, Ross ME: **Calcium-dependent interaction of Lis1 with IQGAP1 and Cdc42 promotes neuronal motility.** *Nat Neurosci* 2006, **9**:50-57.
37. Keays DA, Tian G, Poirier K, Huang GJ, Siebold C, Cleak J, Oliver PL, Fray M, Harvey RJ, Molnar Z *et al.*: **Mutations in alpha-tubulin cause abnormal neuronal migration in mice and lissencephaly in humans.** *Cell* 2007, **128**:45-57.
38. Kumar RA, Pilz DT, Babatz TD, Cushion TD, Harvey K, Topf M, Yates L, Robb S, Uyanik G, Mancini GM *et al.*: **TUBA1A mutations cause wide spectrum lissencephaly (smooth brain) and suggest that multiple neuronal migration pathways converge on alpha tubulins.** *Hum Mol Genet* 2010, **19**:2817-2827.
39. Jaglin XH, Poirier K, Saillour Y, Buhler E, Tian G, Bahi-Buisson N, Fallet-Bianco C, Phan-Dinh-Tuy F, Kong XP, Bomont P *et al.*: **Mutations in the beta-tubulin gene TUBB2B result in asymmetrical polymicrogyria.** *Nat Genet* 2009, **41**:746-752.
- Together with [46*,49*] this study supports the hypothesis that some forms of polymicrogyria and cobblestone cortex may be related migration defects due to disruption in the radial glia scaffold. Compare figure 1 o-r to figures 4-5 in [46*] and figures 5-6 in [49*].
40. Abdollahi MR, Morrison E, Sirey T, Molnar Z, Hayward BE, Carr IM, Springell K, Woods CG, Ahmed M, Hattingh L *et al.*: **Mutation of the variant alpha-tubulin TUBA8 results in polymicrogyria with optic nerve hypoplasia.** *Am J Hum Genet* 2009, **85**:737-744.
41. Tischfield MA, Baris HN, Wu C, Rudolph G, Van Maldergem L, He W, Chan WM, Andrews C, Demer JL, Robertson RL *et al.*: **Human TUBB3 mutations perturb microtubule dynamics, kinesin interactions, and axon guidance.** *Cell* 2010, **140**:74-87.
42. Poirier K, Saillour Y, Bahi-Buisson N, Jaglin XH, Fallet-Bianco C, Nabbout R, Castelnau-Ptakhine L, Roubertie A, Attie-Bitach T, Desguerre I *et al.*: **Mutations in the neuronal ss-tubulin subunit TUBB3 result in malformation of cortical development and neuronal migration defects.** *Hum Mol Genet* 2010, **19**:4462-4473.
43. Leventer RJ, Jansen A, Pilz DT, Stoodley N, Marini C, Dubeau F, Malone J, Mitchell LA, Mandelstam S, Scheffer IE *et al.*: **Clinical and imaging heterogeneity of polymicrogyria: a study of 328 patients.** *Brain* 2010, **133**(Pt 5):1415-1427.
44. Barkovich AJ: **MRI analysis of sulcation morphology in polymicrogyria.** *Epilepsia* 2010, **51**(Suppl. 1):17-22.
45. Piao X, Hill RS, Bodell A, Chang BS, Basel-Vanagaite L, Straussberg R, Dobyns WB, Qasrawi B, Winter RM, Innes AM *et al.*: **G protein-coupled receptor-dependent development of human frontal cortex.** *Science* 2004, **303**:2033-2036.

46. Li S, Jin Z, Koirala S, Bu L, Xu L, Hynes RO, Walsh CA,

- Corfas G, Piao X: **GPR56 regulates pial basement membrane integrity and cortical lamination.** *J Neurosci* 2008, **28**:5817-5826.

This article describes the initial findings in a mouse model deficient for the polymicrogyria gene *Gpr56* and identifies a defect in glial scaffold structure and cortical lamination similar to those observed *TUBB2B* mutations [39**] and cobblestone lissencephaly models [49*].

47. Beltran-Valero de Bernabe D, Currier S, Steinbrecher A, Celli J, van Beusekom E, van der Zwaag B, Kayserili H, Merlini L, Chitayat D, Dobyns WB *et al.*: **Mutations in the O-mannosyltransferase gene POMT1 give rise to the severe neuronal migration disorder Walker-Warburg syndrome.** *Am J Hum Genet* 2002, **71**:1033-1043.

48. Moore SA, Saito F, Chen J, Michele DE, Henry MD, Messing A, Cohn RD, Ross-Barta SE, Westra S, Williamson RA *et al.*: **Deletion of brain dystroglycan recapitulates aspects of congenital muscular dystrophy.** *Nature* 2002, **418**:422-425.

49. Satz JS, Ostendorf AP, Hou S, Turner A, Kusano H, Lee JC, Turk R, Nguyen H, Ross-Barta SE, Westra S *et al.*: **Distinct functions of glial and neuronal dystroglycan in the developing and adult mouse brain.** *J Neurosci* 2010, **30**:14560-14572.

In a conditional mouse model for cobblestone lissencephaly, the authors dissect the relative roles of dystroglycan in the radial glial scaffold and in neurons, showing how radial glia integrity is necessary for the cortical lamination defects and neuronal overmigration observed in this disorder.

50. Jansen A, Andermann E: **Genetics of the polymicrogyria syndromes.** *J Med Genet* 2005, **42**:369-378.

51. Jaglin XH, Chelly J: **Tubulin-related cortical dysgeneses: microtubule dysfunction underlying neuronal migration defects.** *Trends Genet* 2009, **25**:555-566.

52. Zarbalis K, Siegenthaler JA, Choe Y, May SR, Peterson AS, Pleasure SJ: **Cortical dysplasia and skull defects in mice with a *Foxc1* allele reveal the role of meningeal differentiation in regulating cortical development.** *Proc Natl Acad Sci USA* 2007, **104**:14002-14007.

53. Hecht JH, Siegenthaler JA, Patterson KP, Pleasure SJ: **Primary cellular meningeal defects cause neocortical dysplasia and dyslamination.** *Ann Neurol* 2010, **68**:454-464.

54. Walsh CA, Engle EC: **Allelic diversity in human developmental neurogenetics: insights into biology and disease.** *Neuron* 2010, **68**:245-253.