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Malformations of Cortical Development and Epilepsy

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Malformations of cortical development (MCDs) are an important cause of epilepsy and an extremely interesting group of disorders from the perspective of brain development and its perturbations. Many new MCDs have been described in recent years as a result of improvements in imaging, genetic testing, and understanding of the effects of mutations on the ability of their protein products to correctly function within the molecular pathways by which the brain functions. In this review, most of the major MCDs are reviewed from a clinical, embryological, and genetic perspective. The most recent literature regarding clinical diagnosis, mechanisms of development, and future paths of research are discussed.

Malformations of cortical development (MCDs) are common causes of medically refractory epilepsy, particularly in children (Barkovich et al. 2012). Although most childhood epilepsies respond to treatment, ~15% are resistant to pharmacologic treatments (drug-resistant childhood epilepsies) (Guerrini 2006); ~40% of these are caused by MCDs (Kuzniecky et al. 1993b; Frater et al. 2000; Pasquier et al. 2002). One type of MCD, called focal cortical dysplasia (FCD), has an incidence of 50/100,000/yr in children <16 yr of age, adding up to ~0.8% of children (Nelligan and Sander 2011; Ngugi et al. 2011). Approximately 25% (range 10%–30%) of patients with FCD

progress to intractable epilepsy, enriched in those with focal epilepsies (Braathen and Theorell 1995; Wirrell et al. 2013). FCDs of all types are seen in 25%–100% of brain tissue from epilepsy surgery (Mischel et al. 1995; Tassi et al. 2002). Not all people with MCDs have epilepsy, however; presentations typically include variable levels of motor or cognitive impairment, but some are discovered incidentally after magnetic resonance (MR) scans for other medical conditions or unrelated events (e.g., injuries) (de Wit et al. 2008), whereas an unknown number are probably never detected.

Although MCDs have been known for many years and classified for ~20 years, the basic ge-

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netic and molecular processes that underlie the development of these disorders has become much clearer in the past few years. The purpose of this review is to discuss the current classification and molecular underpinnings of these disorders. In doing so, we will concentrate on new concepts that have developed as a result of recent discoveries in the field.

FRAMEWORK OF THE CLASSIFICATION

In the initial classification in which the term “malformation of cortical development” was derived (Barkovich et al. 1996), the investigators separated the disorders into three main groups, based on the earliest stage development that is affected (recognizing that alteration of early developmental events often affects later events, as well): disorders caused by abnormal cell proliferation, abnormal neuronal migration, and abnormal postmigrational cortical development. The discovery of many genes, proteins, and pathways involved in these steps, however, has made the classification more complex in some areas and more simplified in others. In this review, we will first discuss the fundamental concepts underlying each major component of the classification, followed (when appropriate) by a discussion of new discoveries regarding gene mutations, the effects of these mutations on the function of their protein products, the consequent effects on molecular pathways, and how alterations of pathways affect brain development. In areas in which new discoveries have been few, and which, consequently, remain poorly understood, we will discuss potential reasons for the poor understanding.

MALFORMATIONS SECONDARY TO ABNORMAL CELL PROLIFERATION OR APOPTOSIS

A good deal of new information has become available over the past few years with regard to malformations in this category, in particular, pertaining to reduced cell proliferation (microcephalies) (Thornton and Woods 2009; Alkuraya et al. 2011; Bakircioglu et al. 2011; Bicknell

et al. 2011) and malformations associated with abnormal cell proliferation (type II FCDs) (Blümcke et al. 2011), gangliogliomas (Boer et al. 2010; Koelsche et al. 2013), tuberous sclerosis complex (TSC) (Crino 2013), and megalencephalies associated with cerebral dysgeneses (Kurek et al. 2012; Lee et al. 2012; Riviere et al. 2012).

Microcephalies

Our understanding of microcephalies has increased greatly in the past few years with the discovery of the responsible genes and the functions of their protein products. Most of the responsible genes function in cell replication. For example, patients with microcephaly associated with osteodysplastic primordial dwarfism (MOPD), such as Meier–Gorlin syndrome, have mutations affecting subunits of the origin recognition complex, which is loaded onto chromatin at DNA origins before the S phase of mitosis to license replication; in conjunction with additional components CDC6, CDT1, and MCM2–7, it forms the prereplication complex, which initiates DNA replication (Bicknell et al. 2011). Other genes that, when mutated, result in microcephaly include those involved in microtubule formation (*TUBA1A*, *TUBB2B*, *TUBB3*, *TUBG1*) (Poirier et al. 2010, 2012, 2013; Cushion et al. 2013), those coding for microtubule-associated proteins (*DYNC1H*, *KIF5C*, *NDE1*) (McKenney et al. 2010; Alkuraya et al. 2011; Bakircioglu et al. 2011; Poirier et al. 2013), those involved in spindle organization and positioning (*ASPM*) (Desir et al. 2008; Passetard et al. 2009), those regulating centriole length (*CENPJ*) (Tang et al. 2009; Al-Dosari et al. 2010) or centrosome integrity (*STIL*) (Castiel et al. 2011), those that repair genomic defects and regulate genomic integrity (*CEP152*) (Kalay et al. 2011), and many others involved in the very complex process of cell replication. By a combination of clinical characteristics (Mahmood et al. 2011), imaging characteristics (Fig. 1) (Barkovich et al. 2012), and family histories, many of the causes of microcephalies can now be identified in families.

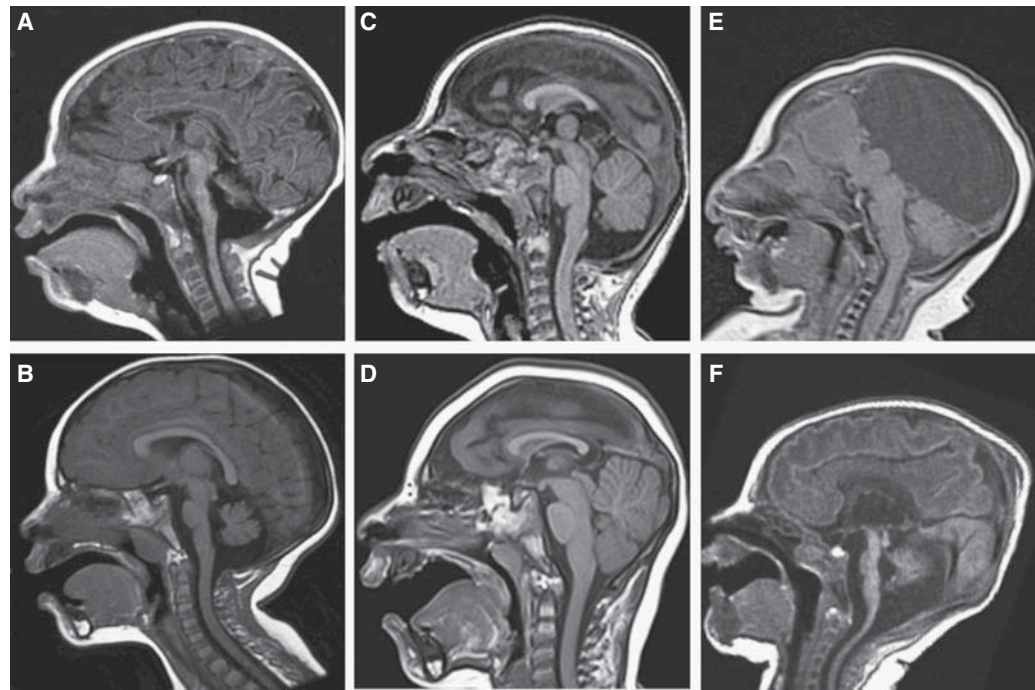


Figure 1. Sorting of microcephalies by morphologic characteristics. (A) Microcephaly with extremely small cerebellum and small pons. (B) Microcephaly with cerebellum and pons that are proportional and slightly disproportionately small compared with cerebrum. (C) Profound microcephaly with proportional cerebellum and brainstem that are disproportionately large compared with cerebrum. (D) Severe microcephaly with brainstem that is disproportionately large compared with cerebrum and cerebellum that is disproportionately large compared with brain stem. (E) Microcephaly with absence of the corpus callosum, interhemispheric cyst, and proportional brain stem and cerebellum with cerebrum; posterior fossa structures appear small because of mass effect from the supratentorial cyst. (F) Microcephaly with simplified cerebral gyral pattern, callosal hypoplasia, and severely disproportionately small brain stem and cerebellum.

Malformations that May Be Associated with Mutations Affecting the Mammalian Target of Rapamycin (mTOR) Pathway

For many years, several malformations caused by abnormal cell proliferation were thought to be related because of their similar histological appearances and MR imaging patterns (Barkovich et al. 2012). These included the brain lesions associated with TSC, a localized enlargement of dysmorphic and dysplastic brain called hemimegalencephaly (HME; also referred to as dysplastic megalencephaly), tumors with dysplastic features (*ganglioglioma*), and focal cortical dysplasia type IIb (FCD IIb) all are characterized by localized dysplastic, enlarged neurons, impaired

myelination, and large, ovoid dysmorphic cells with laterally displaced nucleus and limited axons and dendrites called balloon cells (HMEs), giant cells (TSCs), or atypical ganglion cells (ATGCs) (gangliogliomas). In the past 2 years, it has become clear that all of these disorders, as well as others classified as malformations, as a result of abnormal cell proliferation, result from mutations affecting mTOR signaling pathways (Fig. 2). The mTOR signaling cascade functions as a central controller of organism growth and homeostasis; it integrates the input from upstream pathways, including insulin, growth factors (such as insulin-like growth factor [IGF]-1 and IGF-2), and amino acids and senses cellular nutrient, oxygen, and energy levels. Messenger RNA (mRNA) translation is suppressed in un-

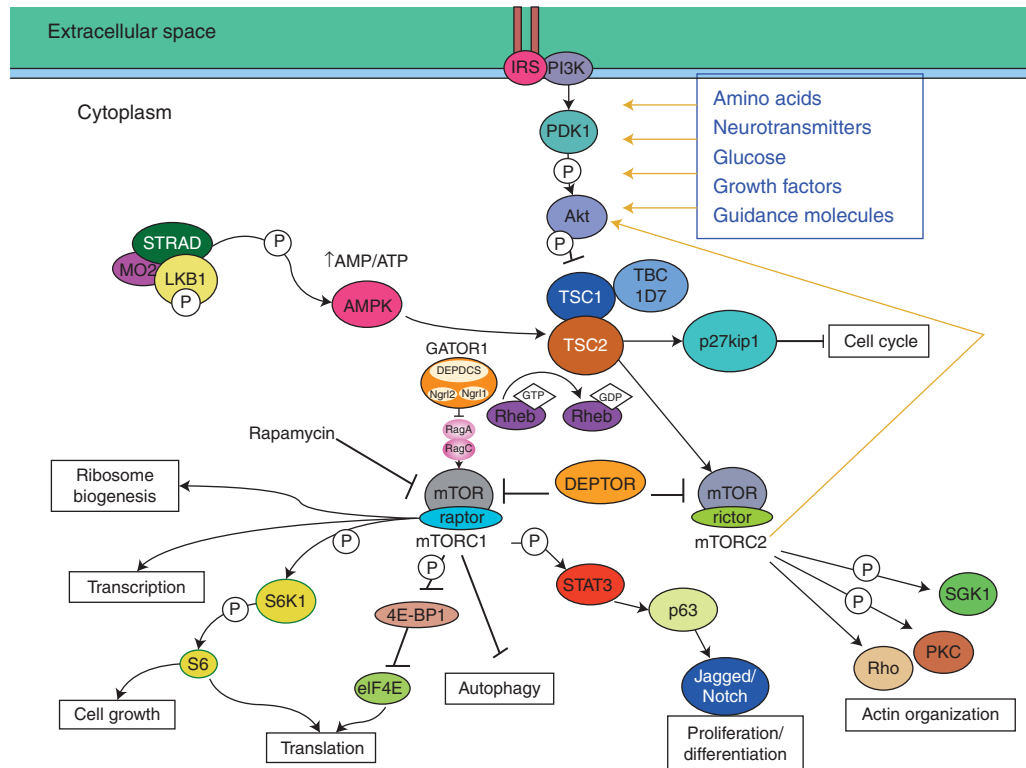


Figure 2. Diagram of portions of the mammalian target of rapamycin (mTOR) pathways associated with many aspects of cerebral cortical development, including transcription, cell growth, translation, proliferation/differentiation, and actin organization. As far as currently known, mTOR complex 1 (mTORC1) is more highly associated with cortical development than mTOR complex 2 (mTORC2). (Adapted from Lim and Crino 2013.)

favorable conditions, whereas translation, transcription, and (consequently) growth are stimulated under favorable conditions (Zoncu et al. 2011; Thoreen et al. 2012). mTOR is the catalytic subunit of two distinct complexes called mTOR complex 1 (mTORC1) and complex 2 (mTORC2), which are distinguished by accessory proteins of mTOR. The molecular details of these signaling pathways can be found in many recent publications (Zoncu et al. 2011; Thoreen et al. 2012; Laplante and Sabatini 2013). An important concept is that the mTOR pathway can be activated or inhibited by a number of upstream signaling mechanisms, such as the insulin/phosphoinositide-3-kinase (PI3K)/AKT pathway or the adenosine monophosphate-activated protein kinase (AMPK) pathway, in response to environmental cues or metabolic demands (Zoncu et al. 2011; Thoreen et al. 2012;

Laplante and Sabatini 2013). The involvement of the mTOR pathway in regulating growth and proliferation of cells in the central nervous system (CNS) makes it a strong candidate to account for the abnormal cellular phenotypes (and, in some cases, increased proliferation) found in type II FCD (Blümcke et al. 2011), dysplastic (hemi)megalencephaly (Flores-Sarnat et al. 2003), ganglioglioma (Boer et al. 2010; Koelsche et al. 2013), and TSC (Tsai et al. 2012; Prabowo et al. 2013). Clinical presentation varies with the type of malformation, ranging from infantile spasms with a burst suppression pattern and/or hemihypsarhythmia on sleep electroencephalography (EEG) in the most severe cases to developmental delay with mental retardation and intractable partial motor or asymmetric tonic or clonic generalized seizures to isolated focal seizure disorders. Brain dysgenesis

may be isolated or seen in conjunction with a neurocutaneous syndrome, such as TSC, hypomelanosis of Ito, or epidermal nevus syndrome (Bulteau et al. 2013).

Recent publications have implicated mutations of a number of genes involved in the mTOR pathways in the pathogenesis of malformations secondary to abnormal cell proliferation. These include *PI3K* and *AKT3* in dysplastic megalencephaly (DMEG) (Lee et al. 2012; Poduri et al. 2012), mutations of *AKT3* and *PIK3R2* in megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH) syndrome (Riviere et al. 2012), mutations of *PIK3CA* in megalencephaly-capillary malformation (MCAP) syndrome (Lee et al. 2012), and congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE) syndrome (Kurek et al. 2012). The work on *AKT3* (Poduri et al. 2012) is particularly compelling for control of proliferation (and, consequently, brain size) as the mouse *Akt3* knockout (KO) model shows selective reduction in brain size because of decreased neuronal number and size (Easton et al. 2005), whereas mice with activating mutations of the kinase domain of *Akt3* show enlarged hippocampi (Tokuda et al. 2011) and humans with duplications or activating point mutations had hemispheric brain overgrowth (Poduri et al. 2012). More important is the observation that these mutations are somatic (not present in other family members) and mosaic (they are present in only a subset of cells of the affected individual). Therefore, genetic testing of other family members will not be helpful and testing of skin or blood cells of affected individuals may not show the mutation responsible for the brain malformation. Indeed, the observation that only a subset of cells contains the mutation in DMEG, in which the entire hemisphere is typically malformed, suggests that both cell-autonomous and non-cell-autonomous mechanisms are at work (Lim and Crino 2013; Poduri et al. 2013). In contrast, germline mutations of *TSC1* or *TSC2* are present in patients with TSC, and recent investigations have shown activation of the mTORC1 and mTORC2 pathways in brain lesions of fetuses with TSC (Tsai et al. 2012; Prabowo et al. 2013), yet only a few tubers are

typically present in the brain. This has prompted some investigators to propose a “two-hit” hypothesis, suggesting presence of both germline and somatic mutations with biallelic gene inactivation (Crino et al. 2010; Poduri et al. 2013); other studies suggest that second hits are rare (Qin et al. 2010).

Some investigators have proposed that somatic mutations of mTORC1 pathway genes may be associated with the pathogenesis of FCD II (Lim and Crino 2013). The authors have each experienced a number of patients with, apparently, localized FCD IIb that continued to have refractory seizures after lesionectomy or hemispherotomy to isolate the visible dysplastic tissue. Subsequently, hemispherectomy, in all cases, revealed much more extensive dysplasia than was visible by magnetic resonance imaging (MRI), including balloon cells and large, dysmorphic neurons, as was described previously by D’Agostino et al. (2004). Indeed, imaging studies of DMEG have emphasized the heterogeneity of the findings on MRI (Barkovich and Chuang 1990; Nakahashi et al. 2009) and have shown that the cerebellum may be affected as well (Sener 1997; Di Rocco et al. 2001). These findings suggest that DMEG may be more heterogeneous within the affected hemisphere than has been generally recognized and that FCD II, particularly FCD IIb as it has nearly identical histology, may represent a region of increased severity in a hemispheric disorder. Future studies of FCD II to look for alterations of mTORC1 may be useful in this regard.

Gangliogliomas are interesting lesions from both a developmental and clinical perspective. They are the most common neoplasm associated with pediatric epilepsy and represent 5% of pediatric brain tumors. The tumors are defined histologically by a loss of cortical lamination, proliferation of glial cells, and the presence of dysmorphic neurons and ATGCs. The dysmorphic neurons and ATGCs resemble the cellular morphologies of the dysmorphic neurons and the giant cells/balloon cells seen in TSC, DMEG, and FCD IIb, and the latter cells express similar protein markers, such as Sox2, Oct4, and Klf4 (Orlova et al. 2010). About 30% of gangliogliomas are associated with FCD, which

are either connected to the tumor or directly adjacent to it (Blümcke et al. 2011). Several studies have suggested activation of mTOR pathway in gangliogliomas with p70S6 kinase, S6 phosphorylation, and a protein profile very similar to that of FCD IIb (Boer et al. 2010). In addition, an identical and common somatic V600E mutation in *B-RAF*, a known pathogenic gene for melanoma and papillary thyroid cancer that has been linked to enhanced mTOR signaling via LKB1 and mTORC2/Akt, has been detected in up to 58% of resected specimens, mainly in the neuronal and ATGC components (Chen et al. 2012; Faustino et al. 2012; Koelsche et al. 2013).

MALFORMATIONS SECONDARY TO ABNORMAL CELL MIGRATION

Malformations secondary to abnormal cell migration include heterotopia, lissencephaly, and so-called cobblestone malformations, which result from lack of attachment of radial glial cells (RGCs) to the pial-limiting membrane (PLM) and consequent gaps in that membrane.

Malformations Secondary to Tubulin and Microtubule-Associated Protein Anomalies

Microtubules are of critical importance in brain development. They are essential in steps of “cell proliferation” (mitosis) and “neuronal migration” (critical in the extension of the leading processes of migrating neurons and interkinetic nuclear migration (McKenney et al. 2010; Kuijpers and Hoogenraad 2011; Huang et al. 2012) in the cerebrum, cerebellum, and brain stem. Microtubules also play critical roles in “axonal path finding” (a process similar to the extension of leading processes of migrating neurons) (Dent et al. 2011). As a result, abnormalities of microtubule formation (tubulinopathies) are typically characterized in the brain by microcephaly, abnormalities of neuronal migration (resulting in gray matter heterotopia or cortical dysgenesis/lissencephaly in the cerebrum and hypoplasia/dysgenesis of the cerebellum), anomalies of axonal pathfinding (diminished white matter volume, corpus callosum

dysgenesis, cranial nerve hypoplasia or aplasia, olfactory nerve/sulcus dysgenesis, and malformations of the brain stem), or a combination thereof (Bahi-Buisson et al. 2008, 2013; Kumar et al. 2010; Tischfield et al. 2010; Guerrini et al. 2012; Chew et al. 2013; Cushion et al. 2013; Poirier et al. 2013; Saillour et al. 2013).

Recent classifications of malformations secondary to abnormal neuronal migration have listed classic lissencephalies (agyria-pachygyria) and variant lissencephaly (caused by *ARX* and *Reelin* pathway mutations) as the two principal categories. Recent work, however, has shown that all of the six grades of classic lissencephalies (Table 1) are caused by mutations of genes encoding tubulins (primarily *TUBA1A*) (Poirier et al. 2007) or proteins that function in conjunction with microtubules (microtubule-associated proteins or MAPs, such as DCX, LIS1, cytoplasmic dynein, kinesins, NudE) (Dobyns et al. 1993; Gleeson et al. 1998; Toyo-oka et al. 2003; Lecourtois et al. 2010; Cushion et al. 2013; Poirier et al. 2013). As mutations of genes encoding tubulins and MAPs are associated with, and likely responsible for, other MCDs (such as heterotopia and polymicrogyria [PMG]-like cortex) (Poirier et al. 2010, 2012; Guerrini et al. 2012; Cushion et al. 2013), one might consider altering the classification to make malformations

Table 1. Grading system for classic lissencephalies

Gradient	Grade of severity
1a = p	Complete agyria
2p > a or 2a > p	Diffuse agyria with a few undulations at the frontal or occipital poles
3p > a or 3a > p	Mixed agyria and pachygyria
4p > a or 4a > p	Diffuse pachygyria, or mixed pachygyria and normal or simplified gyri
5a > p (the reverse 5p > a has not been observed)	Mixed pachygyria and subcortical band heterotopia
6p > a or 6a > p	Subcortical band heterotopia only

a, Anterior location of malformation; p, posterior location.

secondary to mutations of tubulin and MAP genes as a major category of MCD with classic lissencephalies as a subcategory. It will be interesting to determine what differences are seen in the mutations of genes coding for MAPs as compared with those coding for the tubulins themselves.

Phenotypes

As mentioned above, the category of classic lissencephaly can be divided into six grades based on the severity of the malformation (Table 1), and examples of all grades of lissencephaly can be found as a result of mutations of genes for tubulins or MAPs (Bahi-Buisson et al. 2008, 2013; Kumar et al. 2010; Guerrini et al. 2012; Cushion et al. 2013; Poirier et al. 2013). The reason for this is that the phenotype resulting from a tubulin mutation depends on the effects of the mutation on the three-dimensional structure of the resultant microtubule (Cushion et al. 2013; Poirier et al. 2013) and its ability to properly interact with specific MAPs or other heterodimers of tubulin A and B (microtubules are long hollow cylinders with walls composed of heterodimers of tubulin A and tubulin B, which polymerize end-to-end to form “protofilaments,” the building blocks for microtubules). Protofilament polymerization and depolymerization are critical steps, along with actin polymerization and depolymerization, in the pathfinding of axonal growth cones and the leading processes of migrating neurons (Marin et al. 2010; Tischfield et al. 2010; Dent et al. 2011). If a mutation alters the speed of polymerization or depolymerization of protofilaments, the growth cones of axons cannot rapidly respond to attractive and repulsive cues in their immediate environment causing misdirection and retraction of growth cones with ultimate hypoplasia of white matter pathways/cranial nerves (leading to olfactory nerve hypoplasia, congenital fibrosis of the extraocular muscles, corpus callosum hypoplasia, lack of separation of caudate and putamen caused by absence of the anterior limb of the internal capsule) (Tischfield et al. 2010; Chew et al. 2013) or ectopic white matter pathways, such as dysgenesis of corpus

callosum or brain stem (Figs. 3 and 4) (Poirier et al. 2013). In contrast, when the mutations affect the binding sites of MAPs or other proteins that affect the interaction of MAPs with the microtubules (for example, altering binding of LIS1 to its binding site impairs the function of cytoplasmic dynein in interkinetic nuclear migration [Huang et al. 2012; Splinter et al. 2012], which is critical for neuronal migration), the results are pachygyria or frank lissencephaly (Poirier et al. 2013) or, possibly, PMG-like cortex and gray matter heterotopia (Cushion et al. 2013). It is also possible that the impaired migration of neurons to the cortex results in migration of fewer axons, resulting in diminished white matter volume.

Variant Lissencephalies

Lissencephaly can be very different, genetically, clinically, and on imaging, from the classic lissencephaly/pachygyria/band heterotopia spectrum associated with tubulin and MAP abnormalities. In both *ARX* mutations and mutations of the Reelin signaling pathway, affected patients vary widely in clinical severity depending on the gene affected and the severity of the mutation, although most patients have severe, early-onset epilepsy (Hong et al. 2000; Kitamura et al. 2002; Stromme et al. 2002; Kato et al. 2004; Boycott et al. 2005; Glass et al. 2005). Imaging characteristics of these “variant” lissencephalies have fairly distinctive imaging characteristics (of varying severity), which allow identification in most cases; the cerebral cortex is slightly thick (5–7 mm) with an anterior (less severe) to posterior (more severe) gradient, variable hyposulcation, and no cell-sparse zone. *ARX* mutations have absence of the corpus callosum and, typically, small dysplastic basal ganglia (Bonneau et al. 2002), whereas Reelin pathway disorders show cerebellar hypoplasia of varying severity (Hong et al. 2000; Bonneau et al. 2002; Boycott et al. 2005; Glass et al. 2005; Miyata et al. 2009) and granule cell dispersion in the hippocampus (Haas and Frotscher 2010).

Reelin has multiple functions in cerebral development. It acts upstream of Notch signaling, which, in its most classical function, inhibits

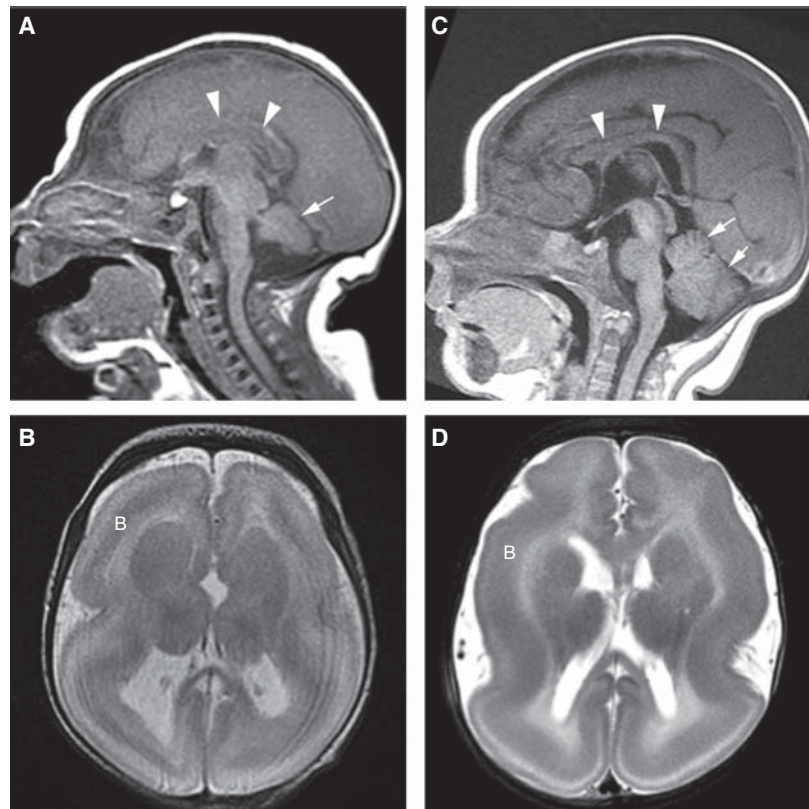


Figure 3. Lissencephaly secondary to *TUBA1A* (A,B) and *LIS1* (C,D) mutations. Note that the child with the *TUBA1A* mutation is smaller, the corpus callosum (arrowheads) is thinner (difficult to see), and the cerebellum is small. Both are characterized by a band (B) of incompletely migrated neurons deep to the cortex.

neural differentiation and maintains neuroepithelial fate, thus, preventing depletion of neuronal precursor cells (Bolós et al. 2007). It also regulates the temporal specification of intermediate precursor cells (IPCs), transformation of radial glia to astrocytes, and controls the translocation of Golgi vesicles into the leading process of migrating neurons, thereby coupling neocortical neurogenesis to neuronal migration and, probably, astrogliogenesis (Lakomá et al. 2011; Meseke et al. 2013a,b). In addition, Reelin acts during the late phases of neuron migration to allow the leading process of a migrating neuron to bypass cortical neurons that have migrated previously. In the mouse, Sekine et al. (2012) have recently defined a large portion of this intracellular pathway, which starts with Reelin binding to Apoer2 and Vldlr, and ends with

change in the conformation of integrin $\alpha5\beta1$ (for details, see Sekine et al. 2012). After this activation, integrin adheres to fibronectin on Cajal–Retzius cells in the molecular zone, allowing the neuron to pass preceding neurons in the primitive cortical zone and enter the outermost submolecular layer currently forming in the cortex (Fig. 5A) (Sekine et al. 2012). In the cerebellum, Purkinje cells form clusters deep within the cerebellar hemispheres until Reelin, secreted by the migrating granule neurons in the external granular layer (D’Arcangelo et al. 1995, 1997), binds to Apoer2 or Vldlr receptors on the Purkinje cells and activates a protein kinase cascade that (ultimately) decreases inter-Purkinje adhesion and allows dispersion of the embryonic clusters. Thus, liberated, the Purkinje cells form their characteristic stripes and begin

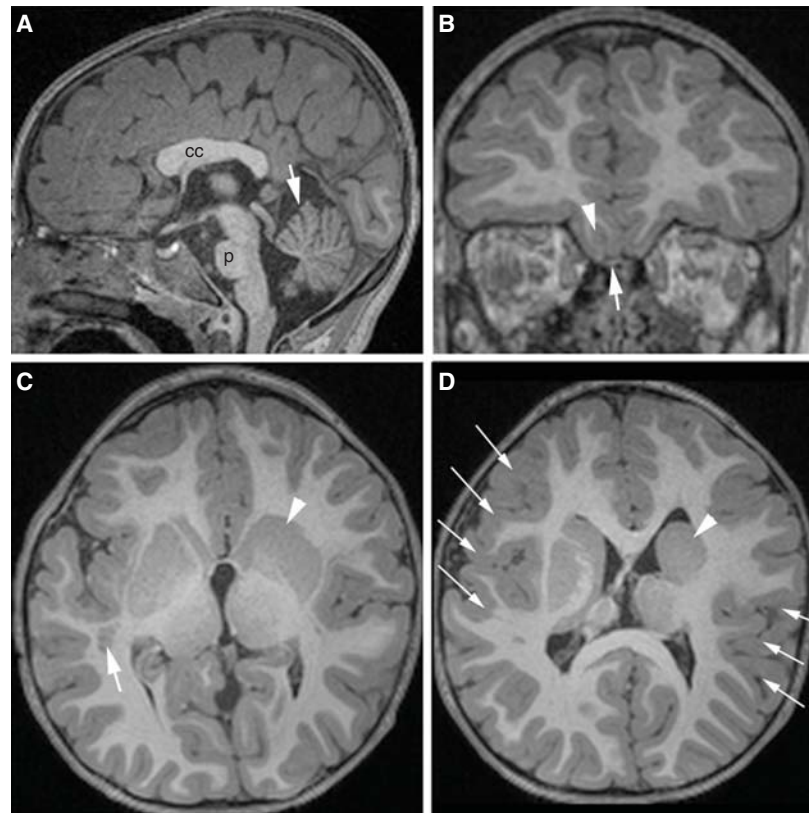


Figure 4. Magnetic resonance imaging (MRI) of patient with TUBB2B mutation showing many aspects of “tubulinopathies.” Sagittal image (A) shows short corpus callosum (cc), small pons (p), and small anterior lobe of cerebellum (white arrow). Coronal image (B) shows normal olfactory sulcus (arrowhead) and bulb (arrow) on the right, but absent sulcus and bulb on the left, an axonal pathfinding disorder. (C) Axial images show gray matter heterotopia (neuronal migration disorder, arrow), absent anterior limb of the internal capsule (axonal pathfinding disorder, arrowheads in C and D), and (D) abnormal sulcation in bilateral perisylvian cortex (arrows).

to establish connections within and outside of the cerebellum (Dastjerdi et al. 2012). Infants with mutations of the Reelin pathway are severely developmentally impaired with marked hypotonia at birth, marked global delays in development, and onset of generalized epilepsy at an early age (Hourihane et al. 1993). The MRI phenotype of Reelin pathway disorders is characteristic (Fig. 5B–D), with some variations, but it is not yet clear whether the variations are more a result of the gene that is mutated or the effect of the mutation on the function of the protein product in the pathway. In addition to the thick cerebral cortex with anterior to posterior gradient, cortical sulcation is simplified, varying

from mild simplification secondary to absence of tertiary cerebral sulci in *VLDLR* mutations to very simplified with only a few, relatively deep sulci present. The cerebellum is small, particularly the vermis, and also has very simplified foliation (completely smooth in severe cases). Hippocampi are incompletely rotated (Hong et al. 2000; Bonneau et al. 2002); this may be related to the severe epilepsy, likely related to developmental dispersion of granule cells in the hippocampi of affected individuals (Haas and Frotscher 2010). We have performed genetic testing on some patients with features suggestive of Reelin pathway abnormalities, but results have been negative. Whether these patients have

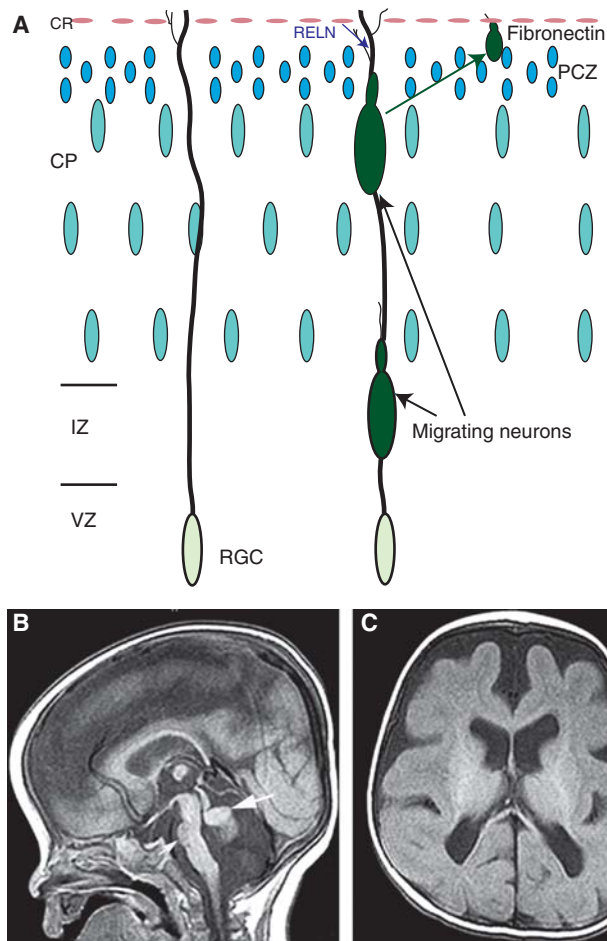


Figure 5. Schematic of Reelin effects on terminal neuronal migration and images of brain with *RELN* mutation. (A) Schematic of neurons migrating along radial glial cell (RGC). The migrating neuron is unable to pass the primitive cortical zone (PCZ) before Reelin (RELN) from the Cajal–Retzius (CR) cells activates the Reelin pathway, resulting in a change in the conformation of integrin $\alpha 5\beta 1$. This integrin is then able to adhere to fibronectin on CR cells in the molecular zone, allowing the neuron to pass through the PCZ and enter the outermost submolecular layer currently forming in the cortex. (B–D) show magnetic resonance imaging (MRI) of an infant with a *RELN* mutation. Note the small, smooth cerebellar vermis (large white arrow in B) and hemispheres (black arrows in D), the small pons (small white arrow in B), and the very simplified cerebral gyral pattern (in C and D) with a thick cerebral cortex (seen best in D).

mutations of Reelin pathway genes that have not yet been identified or whether a similar phenotype may be a result of mutations in other pathways has not been determined.

ARX is an extremely important gene in cortical development as *ARX* regulates genes involved in cell migration, axonal guidance, neurogenesis, and transcription regulation (Colombo et al. 2007; Colasante et al. 2008, 2013;

Fulp et al. 2008; Okazaki et al. 2008), although the mechanisms are not yet known. Because *ARX* interacts with many different targets during development, mutations cause a wide range of abnormalities, including mental retardation (syndromic and nonsyndromic), infantile spasms without brain malformations, dyskinesia, agenesis of the corpus callosum with abnormal genitalia, variant lissencephaly with dys-

morphic basal ganglia, and hydranencephaly (Kato et al. 2004; Okazaki et al. 2008). *ARX* mutants with large deletions, frameshifts, nonsense mutations, and splice site deletions develop a very severe syndrome known as XLAG (X-linked lissencephaly with agenesis of the corpus callosum and abnormal genitalia), which is also associated with abnormalities of the basal ganglia and cerebellum and, in the most serious cases, with hydranencephaly, a disorder in which large portions of the cerebral hemispheres appear to have been destroyed (Kato et al. 2004). Affected patients develop generalized, difficult-to-control seizures in the first hours of life (or before birth), often manifesting tonic spasms of the extremities, severe hypotonia, craniofacial dysmorphism, poor neonatal reflexes, a small penis, and undescended testes (Bonneau et al. 2002).

The cortical malformation in *ARX*-associated lissencephaly has been described as a three-layer cortex in which the number of neurons in the brain is markedly diminished. The outer cortical layer is a rather thick molecular layer that consists mainly of scattered small- to medium-sized neurons (Bonneau et al. 2002; Forman et al. 2005; Okazaki et al. 2008). Immediately below is a hypercellular layer composed of mainly small neurons with a relative increase (compared with layer 1) in pyramidal cells. The third layer is thick, containing sparsely distributed small- and medium-sized neurons, including pyramidal neurons of various sizes; no myelinated axons are detected (Forman et al. 2005; Okazaki et al. 2008). A few scattered neurons and very few myelinated axons are seen in the white matter. Recently, Colasante et al. (2013) reported data suggesting that *Arx* regulates the expansion of both RGCs and, with a more pronounced effect, intermediate progenitor cells and that mutations of *Arx* result in reduced production of both GABAergic and glutamatergic cortical neurons. In addition, they identified a cohort of genes whose expression is consistently altered in the cerebral cortices of *Arx* KO mice compared with wild-type mice (Colasante et al. 2013). Among these genes was *Cdkn1c*, which encodes a member of the Cip/Kip family of cyclin-dependent kinase inhibitors.

CDKN1C antagonized cell-cycle progression by inhibiting G_1/S transition (Sherr and Roberts 1999). They proposed that *ARX* may regulate cortical progenitor pool expansion by repressing expression of *Cdkn1c* in the developing cerebrum. Despite these recent advances, much remains to be understood about the many functions that *ARX* and its loss have on brain development.

Gray Matter Heterotopia

Heterotopia are accumulations of normal-appearing neurons in abnormal locations. They may be isolated or associated with other cerebral or extracerebral disorders. Approximately 90% of patients with the simpler forms of heterotopia (periventricular nodular [PNH; Fig. 6A] and subcortical heterotopia) have epilepsy, which can begin at any age, from infancy to adulthood, although isolated heterotopia may be found incidentally in patients of any age who have MR imaging for unrelated causes. Partial epilepsy with temporo-occipital auras is the most common type (Dubeau et al. 1995, 1999). Localization of the epileptogenic area is complex, as the heterotopia may be functionally active and engage in complex epileptogenic networks that involve the overlying cortex, which is usually reorganized (Preul et al. 1997; Richardson et al. 1998; Mai et al. 2003; Tassi et al. 2005). Although ictal single-photon emission-computed tomography (SPECT) suggests that seizures arise from the heterotopic area (Odabasi et al. 1997), studies with depth electrodes in a few patients with deeply located nodules have shown that seizure activity may originate within both the heterotopic nodule and the overlying cerebral cortex (Tassi et al. 2005), or just within the nodule (Scherer et al. 2005). Patients with band heterotopia (also called laminar heterotopia or double cortex) typically present with epileptic seizures (47%), including infantile spasms or developmental delay (16%) (Barkovich et al. 1994; Bahi-Buisson et al. 2013). Most have intellectual disability with impairments that include abnormal language development and significant behavioral disturbances, such as hyperkinetic movements, crying, and, occa-

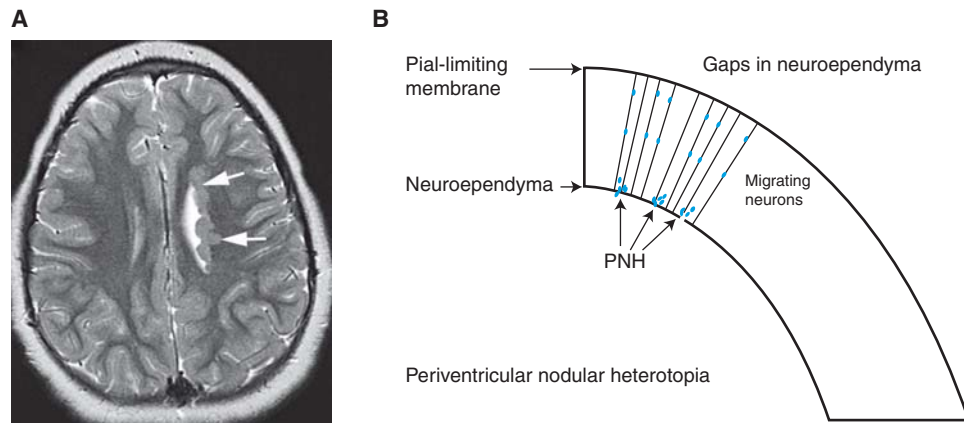


Figure 6. Periventricular nodular heterotopia (PNH). (A) An axial magnetic resonance imaging (MRI) scan shows nodules of gray matter intensity (arrows) along the left lateral ventricles, a characteristic appearance of PNH. (B) A schematic illustrating the mechanism of PNH formation. Disruption of neuroependyma, possibly because of disrupted vesicular trafficking, results in “gaps” in the membrane and disrupted neuroependymal attachment of the radial glial cells (RGCs). Neurons produced in the ventricular zone are not connected to the RGCs and are unable to migrate, remaining at or near the ventricular border as nodules of neurons.

sionally, autistic features (Bahi-Buisson et al. 2013). Rarely, they may develop normally until epilepsy begins in adulthood.

Simple forms of heterotopia, such as PNH, are localized. Typically, a few nodules lie immediately adjacent to the ventricular wall or a few millimeters away from it; the neurons may be arranged in a pattern suggestive of laminar organization (Garbelli et al. 2009), and they contain primarily later-born neurons (Ferland and Guerrini 2009). PNH is often associated with other malformations, which vary with the location of the heterotopia; patients with posterior (trigonal, occipital, and temporal horns) PNH have a high incidence of cerebellar dysgenesis, corpus callosum anomalies, under-rotated hippocampi, and temporal lobe cortical dysgenesis of various types (Pisano et al. 2012; González et al. 2013; Mandelstam et al. 2013). More complex forms include subcortical heterotopia, which are a continuous, often swirling conglomeration of neurons that extend from the ependyma to the cortex; a subset of these contain colony-stimulating factor (CSF) and blood vessels and are continuous with the subarachnoid space (Barkovich 2000). Band heterotopia is best considered a mild form of lissencephaly;

affected patients have a wide range of clinical manifestations that are related to the thickness of the band and the altered sulcation of the overlying cortex (Barkovich et al. 1994).

Neurogenetic analyses have identified two human genes (*FLNA* and *ARFGEF2*) that are known to cause PNH; other genetic abnormalities associated with PNH include duplication of 5p15 (anterior PNH) (Sheen et al. 2003), deletion 6p25 (with white matter anomalies) (Cellini et al. 2012), 7q11.23 (with Williams syndrome) (Ferland et al. 2006; Ramocki et al. 2010), 1p36 monosomy (with corpus callosum agenesis) (Neal et al. 2006; Shiba et al. 2013), 5q14.3-q15 (Cardoso et al. 2009), and 6q terminal deletion (Conti et al. 2013). The most common is inherited in an X-linked-dominant manner from mutations of *FLNA* (Fox et al. 1998). *FLNA* is an actin-binding protein that serves as a scaffold for many proteins; therefore, PNH has been assumed to result solely from impaired neuronal migration from the ventricular and subventricular zones (Fox et al. 1998; Barkovich et al. 2001). However, the discovery that PNH is also found (associated with microcephaly) in patients with mutations of the *ARFGEF2* microcephaly gene (Sheen et al. 2004) has altered this

concept. *ARFGEF2* encodes BIG2 (Brefeldin-A inhibited guanine exchange factor-2), a protein kinase A–anchoring protein that regulates Golgi-vesicle trafficking (Sheen et al. 2004). Ferland and Guerrini (2009) presented strong evidence that PNH is not solely the result of impaired migration, but can arise from defects of the neuroependyma. They suggested that such defects result in impaired adhesion of neural progenitors and radial glial endfeet to the neuroepithelium (neuroependyma), resulting in an inability to engage and migrate along radial glia. Other animal work has shown that mutations of *ARFGEF2* result in an increase in *FLNA* (Zhang et al. 2013). Sheen (2012) has proposed that the underlying problem is alterations of vesicular trafficking, which results in disruption of the neuroependymal continuity after replication and migration of neuroepithelial cells near the ventricular lining. Ependymal disruptions may explain many observed sporadic heterotopia (Fig. 6B).

Cobblestone Malformations

Formerly known as type II lissencephaly (Dambaska et al. 1983; Dobyns et al. 1985) because the outer surface of the brain was rather smooth (with small surface bumps from the presence of neurons in the subarachnoid spaces), the true nature of cobblestone malformations began to be evident after the discovery that many of the affected patients had congenital muscular dystrophies, associated with elevated serum creatine kinase levels, hypotonia, and, often, cardiac involvement after the first decade. Affected patients also have ocular anomalies, including myopia, cataracts, retinal detachment, microphthalmia, buphthalmos, persistent hyperplastic primary vitreous, or congenital glaucoma. Medically refractory epilepsy is seen in some forms (Di Rosa et al. 2011; Barone et al. 2012), but is uncommon.

When MRIs of affected patients began to be performed, they showed cerebral cortical dysgenesis, abnormalities of myelination, and marked disturbances of brain stem and cerebellar development (Van der Knaap et al. 1997; Barkovich 1998). The brain, muscle, and ocular

anomalies all result from abnormal linkage of basement membrane to muscle cells or (in the brain and eye) radial glia transporting migrating cells (de Bernabe et al. 2003; Beltran-Valero de Bernabe 2004; van Reeuwijk et al. 2005, 2006, 2007, 2010). As the linkages seemed to depend on glycosylation of α -dystroglycan (α -DG) on the muscle fibers/radial glial endfeet, these disorders became known as dystroglycanopathies (Martin 2005), although the term “cobblestone malformation” is currently preferred. In the brain, abnormal glycosylation of α -DG on the radial glial endfeet was found to be associated with defects of the PLM (also called the glia limitans) (Myshrrall et al. 2012), and with abnormal connection of the radial glia to the membrane. Mutations of laminins, the receptors for α -DG in the PLM, are another cause of cobblestone malformations (Vigliano et al. 2009; Barak et al. 2011; Radmanesh et al. 2013; Radner et al. 2013), as are mutations of *GPR56* (also located on radial glia endfeet) and its collagen receptors in the PLM (Li et al. 2008; Bahi-Buisson et al. 2010; Labelle-Dumais et al. 2011; Luo et al. 2011, 2012).

Clinical phenotypes vary widely and correlate less with the mutated gene than with the effect of the specific mutation on the RGC–PLM linkage and the integrity of the PLM. The severity and clinical phenotypes of these disorders are very variable, ranging from the Walker–Warburg phenotype (severe brain dysgenesis with associated hydrocephalus, and severe ocular anomalies) to the Fukuyama phenotype (with much less severe brain and ocular anomalies) to patients with findings limited to congenital muscular dystrophy, mental retardation, and cerebellar cysts (Topaloglu et al. 2003; Barkovich et al. 2012). In addition, MRI phenotypes vary, with some cobblestone malformations having an irregular, bumpy (microgyric-appearing) inner and outer cortical surface (Fig. 7A), whereas others have a rather smooth (“lissencephalic”) subpial surface, resulting from columns of neurons extending perpendicular to the cortical surface for variable depths into the underlying white matter (Fig. 7B). This difference appears to be a result of the amount of tissue in the “extracortical

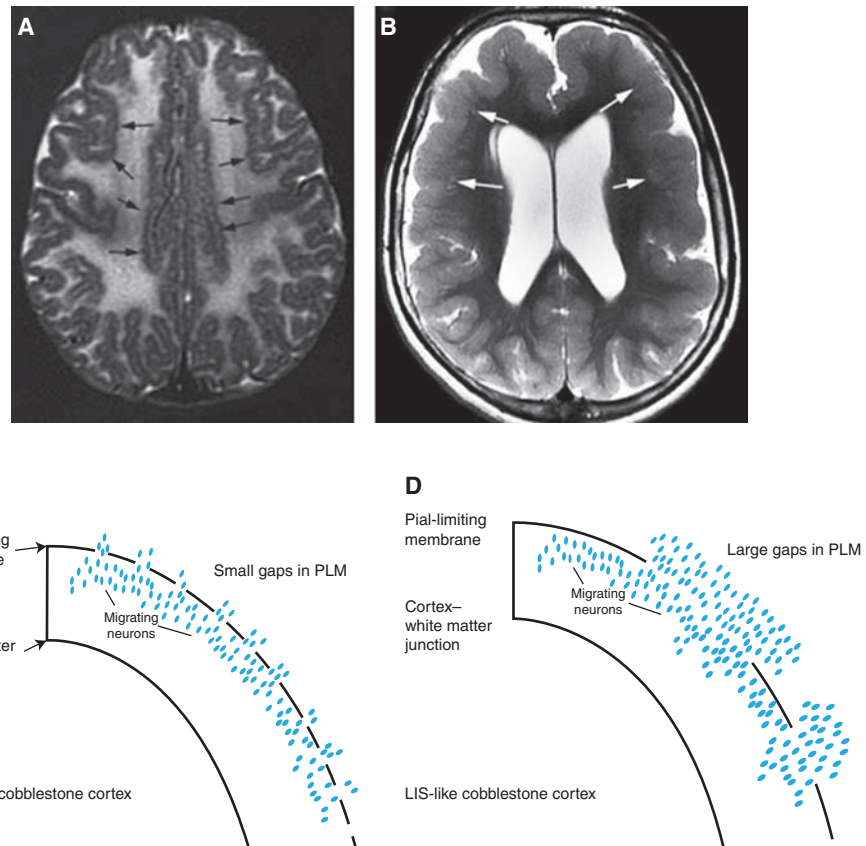


Figure 7. Cobblestone malformations. Phenotypes of cobblestone malformations vary with small, dysmorphic cerebella and brain stems (not shown) in addition to the cortical malformations. The latter may show (A) a microgyric pattern (black arrows), or (B) a pachygyric, lissencephalic-like pattern (white arrows). It is postulated that the former pattern results from (C) migration of relatively few neurons through small gaps in the pial limiting membrane, while the latter results from (D) larger gaps and greater number of neurons migrating into the subarachnoid space.

layer” (the name given to the cells that migrate through the gaps in the PLM and into the subarachnoid space), which is, in turn, related to the size of the gaps in the PLM (Fig. 7C,D) (Devisme et al. 2012). Although it is likely related to the lack of linkage of the RGCs to the PLM, the precise cause of the gaps in the PLM remains unknown. Moreover, many patients in this spectrum of disorders remain unclassified and much work remains: to define unknown RGC–PLM linkages and their molecular components, to determine why cortical malformations in some have an anterior-to-posterior gradient and others are predominantly posterior, to understand the cause of the associated

myelination deficits, and to develop potential therapies.

MALFORMATIONS SECONDARY TO ABNORMAL POSTMIGRATIONAL CORTICAL DEVELOPMENT

PMGs

PMG is a term used to describe malformations characterized by an excessive number of small and prominent convolutions spaced out by shallow and enlarged sulci; the pathologic hallmark is fusion of the molecular layer of the cortex above the microgyri (Friede 1989; Jud-

kins et al. 2011). It may develop nearly anywhere in the cerebral cortex, with many cases resulting from prenatal ischemic, teratogenic, or infectious brain injury (Friede 1989; Norman et al. 1995). PMG may be isolated or associated with other brain malformations, most commonly PNH (Wieck et al. 2005) or schizencephaly (Barkovich and Kjos 1992; Barkovich et al. 2012). Indeed, schizencephaly may be considered a severe variant of PMG, which is likely to be acquired (Barkovich and Kjos 1992; Barkovich et al. 2012), and is associated with young maternal age, absence of prenatal care, alcohol use, and non-CNS anomalies that are likely secondary to vascular disruption (Curry et al. 2005; Dies et al. 2013); genetic causes seem to be very rare. PMG is seen in a wide number of patterns and syndromes (Barkovich 2010; Leventer et al. 2010) and is associated with mutations in several genes (Guerrini and Parrini 2010). The spectrum of associated clinical manifestations is very wide, ranging from severe early-onset encephalopathy with spastic quadriplegia, profound retardation, and intractable epilepsy to normal individuals with selective impairment of higher-order neurological functions (Galaburda et al. 1985; Cohen et al. 1989). PMG syndromes (Barkovich et al. 1999) are based on lobar topography of the malformation and include bilateral perisylvian PMG (Kuzniecky et al. 1993a), bilateral frontal PMG (Guerrini et al. 2000), bilateral parasagittal parieto-occipital PMG (Guerrini et al. 1997), and multilobar PMG (Guerrini et al. 1998). Most cases of these disorders are sporadic, but some families have been reported. In particular, autosomal recessive bilateral frontoparietal PMG has also been described, but is currently considered to be a cobblestone malformation (Li et al. 2008; Bahi-Buisson et al. 2010; Barkovich et al. 2012). In addition, some appear to have rather distinctive clinical manifestations, which seem to reflect the regions of the cerebrum affected.

The perisylvian region is, by far, the most common location for PMG (Hayashi et al. 2002; Leventer et al. 2010), and it is not surprising that “bilateral perisylvian PMG” is, by far, the most common bilateral PMG syndrome (Leventer et al. 2010). The affected cortex is sometimes

restricted to the areas surrounding the sylvian fissures bilaterally, but may extend superiorly over the convexity, and anteriorly or posteriorly nearly as far as the frontal and occipital poles. Analysis of such cases shows a tapering of the PMG as the malformation extends away from the perisylvian region (Leventer et al. 2010). The medial surfaces of the cerebral hemispheres are rarely involved. More extensive involvement is associated with poorer motor and cognitive outcomes (Gropman et al. 1997; Clark et al. 2006). Some cases show marked asymmetry of involvement, with a striking (80%) predisposition for the right hemisphere; these are frequently associated with deletions of chromosome 22q11.2 (Sztriha et al. 2004; Chang et al. 2006; Robin et al. 2006). A missense mutation of the *SRPX2* gene at Xq22 was reported in an affected male, and this may explain the associated facio-pharyngo-glosso-masticatory diplegia with dissociation of automatic (preserved) and voluntary (impaired) facial motility described in some affected patients (Guerrini et al. 1992; Kuzniecky et al. 1993a). Seizures are very common, typically beginning in the second half of the first decade, and are poorly controlled in ~65%; atypical absences, tonic or atonic drop attacks, and tonic-clonic seizures are most frequent, often occurring as Lennox–Gastaut-like syndromes. A minority has partial seizures, typically involving facial muscles (Guerrini et al. 1992; Kuzniecky et al. 1994; Gropman et al. 1997). Other forms of bilateral symmetrical PMG are much less common, have not been associated with specific genes or mutations, and will not be discussed. Unilateral PMG is a relatively frequent cause of epilepsy with continuous spikes and waves during sleep, which has a variable duration and consequences on cognitive abilities, but an invariably favorable seizure outcome (Guerrini et al. 1998).

PMG is poorly understood from a brain developmental perspective, partly because the term has been used imprecisely in the literature, and partly because many different processes can result in a thin cortex with many small sulci/gyri: shunted brains of infants born with severe congenital hydrocephalus (stenogyria) (Miller et al. 2008), brains with defects in the PLM (cob-



blestone cortical malformations) (Bahi-Buisson et al. 2010; Devisme et al. 2012), ciliopathies (Giordano et al. 2009; Kheradmand Kia et al. 2012), tubulinopathies (Jaglin et al. 2009; Jansen et al. 2011; Cederquist et al. 2012; Guerrini et al. 2012; Romaniello et al. 2012), inborn errors of metabolism (Gressens et al. 2000; van Straaten et al. 2005), formation of subcortical heterotopia (Barkovich 2000), and many others. Although it has become accepted that stenogyria and cobblestone cortex differ from “true” PMG, the many different types of irregular cerebral cortices that continue to be labeled as PMG cause considerable confusion and have resulted in some investigators creating a category of “PMG-like” malformations (Cushion et al. 2013). Unfortunately, the imaging characteristics of “true” PMG are difficult to determine because surgical/pathological correlation is very uncommon. Pathologists describe “true” PMG as showing cortical lamination defects, in contrast to “microgyria” or “polygyria,” in which a normal six-layer cortex persists (Friede 1989). Recent work has shown that the cortical lamination of PMG varies within patients; so-called “unlayered” (also called two-layer) PMG, classic four-layer PMG, and six-layer PMG (normal neocortical laminar pattern, but showing fusion of the molecular layer) may all be present in a single patient (Judkins et al. 2011). Moreover, neurons seem to be positioned in appropriate laminae, suggesting that PMG is not a migration disorder, but a postmigration disruption with the only defining characteristic being fusion of the molecular layer (Judkins et al. 2011). The challenge at this time would seem to be finding a means other than histology to accurately separate PMG from other types of microgyria to aid in classification and understanding of these many disorders. New MRI techniques show promise in this regard (Im et al. 2012).

CONCLUSION

MCDs are a fascinating, wide-ranging group of disorders, which are common causes of developmental delay and epilepsy. A focus on understanding the molecular pathways that are disturbed in these disorders will allow treatments

to be developed, whereas, at the same time, improving our understanding of brain development.

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