Developmental Genetic Malformations of the Cerebral Cortex

Volney L. Sheen, MD, PhD, and Christopher A. Walsh, MD, PhD

Address
Department of Neurology, Beth Israel Deaconess Medical Center, HIM 816, 4 Blackfan Circle, Boston, MA 02115, USA.
E-mail: cwalsh@bidmc.harvard.edu

Current Neurology and Neuroscience Reports 2003, **3:**433–441
Current Science Inc. ISSN 1528–4042

Cortical malformations give rise to severe clinical manifestations such as epilepsy and mental retardation, but sometimes to more subtle problems like dyslexia. From a clinical standpoint, such structural abnormalities are diagnosed by radiographic and histologic findings, with disease classifications often based on these observations. Using this categorization, many of the responsible genes have been determined and now provide a means of understanding the molecular basis of the neurologic disorders. This review discusses the known genetic developmental syndromes in the context of the observed cortical malformations, the expression and function of the responsible genes, and their potential roles during the various stages of central nervous system development.

Introduction

The human genetics underlying cortical malformations can provide insight into the basis of human disease when compared with the normal development of the central nervous system. Moreover, correlation between the clinical presentation and the responsible genetic mutation involved in human disease inherently provides an understanding of genetic function. More recently, the finding that multiple genes can lead to similar cortical malformation phenotypes has provided a means to focus on biochemical pathways and molecular signaling mechanisms involved in the basic development of the cerebral cortex.

Normal cortical development proceeds through defined periods of neural proliferation within the ventricular zones, departure from the ventricular zone, migration of postmitotic neurons into the cortical plate, and subsequent neuronal differentiation and development of connectivity (Fig. 1A). Disruption of genetic and molecular mechanisms during these stages of cortical development leads to distinct cortical malformations. In this simplified perspective, classification of such disorders based on these distinct intervals provides a framework with which to understand the genetics of developmental syndromes. That said, it is increasingly clear that the function of many genes is not restricted to a single phase of proliferation, migration, or differentiation, and in fact, is more likely to influence several of these developmental processes.

The current review summarizes the known genetic developmental syndromes in the context of their characteristic cortical malformations and how these relate to the potential functions of the responsible genes during the normal development of the nervous system.

Microcephaly Reflects Disordered Proliferation

During the first fetal trimester, the cerebral cortex is formed by the rapid expansion of cerebral cortical neural precursors (Fig. 1B). These precursor cells are located within the neocortical ventricular zone (VZ), which is a transient, pseudo-stratified epithelial layer that lines the lateral ventricles during embryonic development. As precursors progress through the cell cycle, they undergo interkinetic nuclear migration such that the location of a precursor cell's nucleus in the VZ is consistently related to the phase of the cell cycle. Nuclei entering DNA replication in synthesis (S) phase are positioned in the upper half of the epithelium, away from the ventricular surface, whereas cells transitioning from S to growth (G)2 phase have nuclei that translocate toward the ventricular surface, and cells in mitosis (M) phase lie adjacent to the surface. After cell division, precursors that re-enter the cell cycle remain in the ventricular epithelium, but their nuclei translocate toward the pial surface as the cells enter G1 phase [1].

Microcephaly results from any process in which the proper size of the cerebral cortex is not achieved. Numerous disorders in metabolism, cytoplasmic microtubule regulators, secreted factors, transcription factors, protein kinases, and regulators of cholesterol metabolism can disrupt cellular division and lead to microcephaly. Most of the genetic disorders that cause microcephaly are associated with other non–central nervous system (CNS) findings [2,3].

In true microcephaly (microcephaly vera), abnormalities are limited to a congenital reduction in brain size greater than two SD below the mean, and there is gross preservation of brain architecture and no non-CNS findings [2,4]. Thus far, six autosomal recessive microcephaly loci have been mapped, three of which have a

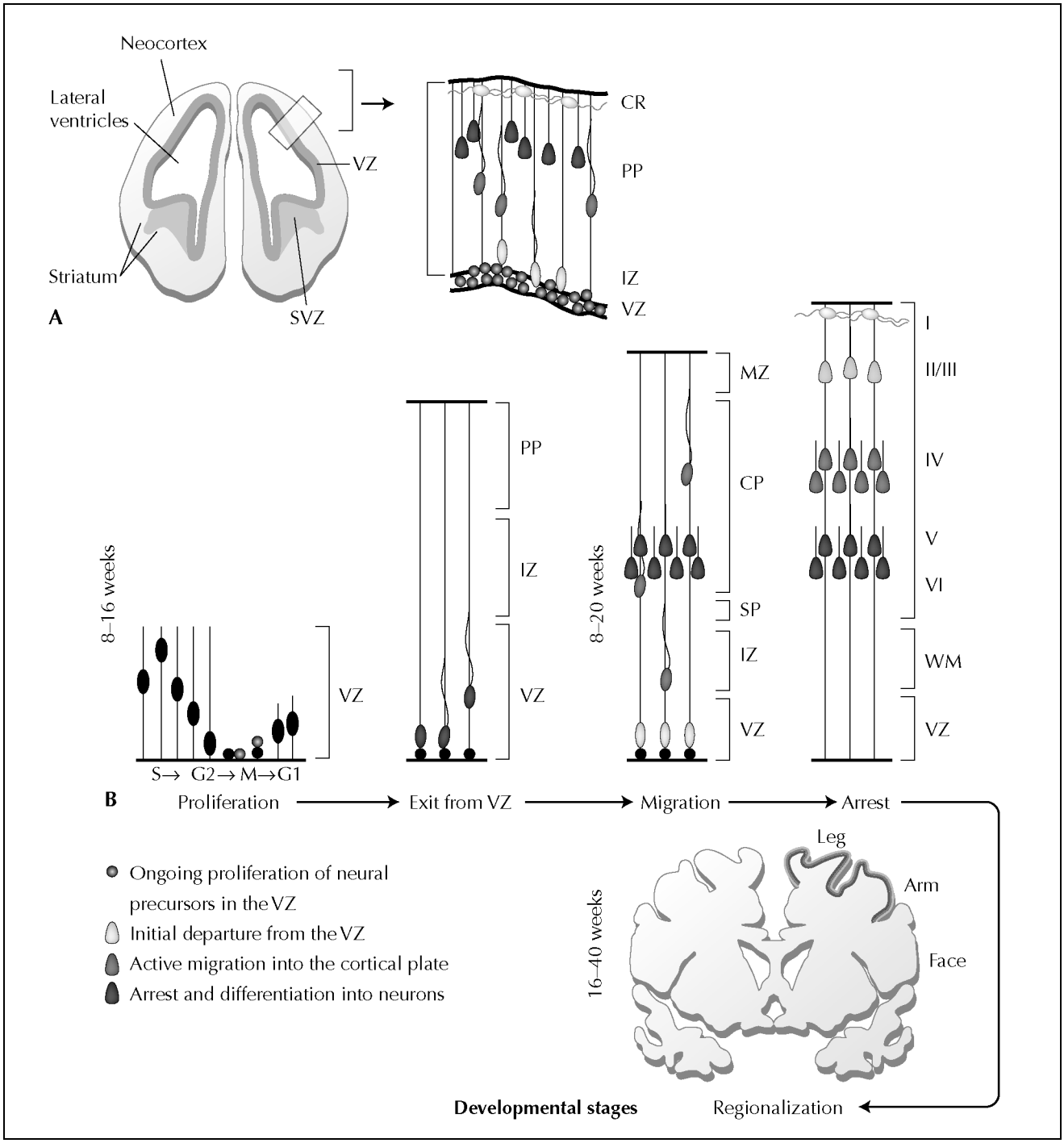

Figure 1. Diagram of the sequential developmental stages of the cerebral cortex. **A,** General anatomic overview of the developing cerebral cortex. Higher magnification diagram (*right*) of inset (*left*) illustrates ongoing proliferation of neural precursors in the VZ (*circles*), initial departure from the VZ (*light gray*), active migration into the cortical plate (*dark gray*) and subsequent arrest and differentiation into neurons *(black*). **B,** Temporal progression of human cerebral cortical development. During the first 8 to 16 weeks of development, neural progenitors undergo proliferation, with the period of neuronal migration extending over 8 to 20 weeks. By 16 to 40 weeks, regional specification with clear formation of sulci and gyri are apparent. Earlier-born neurons (*black*) become situated in deeper cortical layers (V to VI), with later-born neurons (*light gray*) positioned more superficially in layers II to III. (CP—cortical plate; CR—Cajal-Retzius cells; IZ—intermediate zone; MZ—marginal zone; SP—subplate; SVZ—subventricular zone; VZ— ventricular zone.)

known genetic basis. The MCPH1 disorder maps to chromosome 8p23, MCPH2 to 19q13.1-13.2, MCPH3 to 9q34, MCPH4 to 15q, MCPH5 to 1q31, and MCPHA to 17q25 [5]. Recently, identification of genes responsible for some of these syndromes, as well as for other "symptomatic" forms of microcephaly (which generally show non-CNS findings as well) has begun to provide some insights into the genetic control of cerebral cortical size (Table 1).

Disruption of processes involved in cellular division appears to be an important cause of microcephaly. The autosomal recessive microcephaly disorder MCPH5 is caused by a mutation in the abnormal spindle protein (ASPM) [6]. ASPM is a 3477-amino acid protein with 74 'IQ' repeats. IQ repeats represent domains of approximately 20 amino acids in length that begin with isoleucine (I), then glutamine (Q). In some proteins, they bind calmodulin, though their role in ASPM is not known. Remarkably, the number of IQ domains encoded by corresponding ASPM genes increases progressively between flies, mice, and humans, although it is unknown whether the increase in the size of the encoded protein has any functional relationship to the evolutionary increase in brain size. ASPM expression is preferentially restricted to the cerebral cortical ventricular zone during periods of neurogenesis. However, ASPM appears to be expressed in multiple organ systems that show no clear phenotype in patients with ASPM mutations. In *Drosophila*, the ASPM homologue, called abnormal spindle protein (asp), is essential for normal mitotic spindle function in embryonic neuroblasts. The fly asp protein localizes to the centrosome during mitosis and appears to stabilize the tubulin ring complexes that organize the centrosome [7]. In this manner, ASPM might cause microcephaly in humans by perturbing the cell cycle during mitosis and, consequently, the number of neural progenitors generated during development.

The autosomal recessive microcephaly disorder MCPH1 is caused by a mutation in a previously uncharacterized gene that has been dubbed microcephalin [8]. Microcephalin encodes an 835-amino acid protein with three predicted BRCA1 C-terminal (BRCT) domains, which in other related proteins interact to form homo-/hetero-BRCT multimers [9]. Because BRCT domains are present in several key proteins controlling the cell cycle [9] and because microcephalin expression also appears localized to the ventricular neuroepithelial progenitor cells of the developing forebrain [8], cell cycle dysregulation could represent a plausible mechanism for MCPH1 as well. Alternatively, BRCT domains are found in many DNA repair proteins [9], and loss of function of DNA repair genes might lead to excessive apoptotic cell death following neurogenesis [2].

The rapid proliferation of precursors within the VZ requires increased energy demands, suggesting that impairments in metabolism could also lead to microcephaly. The autosomal recessive disorder microcephalia of Amish (MCPHA) is caused by a mutation in SLC25A19, which encodes a widely expressed nuclear mitochondrial deoxynucleotide carrier. This disorder is characterized by severe congenital microcephaly, elevated levels of α-ketoglutarate in the urine, and premature death. Mutations in SLC25A19 result in failure of deoxynucleotide transport across the inner mitochondrial membrane, suggesting a primary metabolic cause of microcephaly [10]. An absence of associated birth defects and a congenital rather than postnatal microcephaly separate this disorder from other inborn errors of metabolism that often cause progressive neuronal degeneration, and suggest that SLC25A19 may be preferentially required during neurogenesis.

Finally, chromosomal breakage represents another apparent cause of microcephaly. Nijmegen breakage syndrome (NBS) maps to chromosome 8q21 and is caused by a mutation in nibrin, a 754-amino acid protein involved in double-stranded DNA repair [11]. Autosomal recessive NBS is characterized by microcephaly, mental retardation, immunodeficiency, and a predisposition to cancer. Nebrin appears to form a complex with MRE11 and RAD50, which together are necessary DNA repair and cell cycle checkpoints [12]. Furthermore, the phosphorylation of nebrin by the ataxia telangiectasia protein (Atm) appears critical for cellular response to DNA damage, suggesting that mutations in these two genes that have common phenotypes also share a common pathway [13].

Periventricular Heterotopia

Periventricular heterotopia (PH) (nodules of neurons along the lateral ventricles) involves disruption of neuronal exit/departure from the ventricular zone. As cortical development proceeds, the progenitor cells of the ventricular epithelium give rise to increasing numbers of postmitotic neurons, and these neurons leave the VZ and migrate outward toward the pia where they form the cerebral cortex (Fig. 1B). This process of radial neuronal migration appears to be frequently disrupted in an increasingly wide array of cerebral cortical malformations.

For example, failure of some postmitotic neurons to depart from the VZ into the cortical plate could give rise to nodules of neurons that line the lateral ventricles beneath an otherwise normal cortex (*ie*, PH) [14]. Thus far, three loci for PH have been identified, two of which have a known genetic basis. The X-linked dominant form of PH maps to chromosome Xq28, an autosomal recessive form to 20q13, and some sporadic cases to 5p15 (Sheen and Walsh, unpublished data) (Table 1) [15-17].

Disruption of some aspect of actin cytoskeletal function is implicated in the major cause of PH. X-linked dominant PH is caused by mutations in the filamin A (FLNA) gene, a 280-kD actin-binding phosphoprotein that is widely expressed throughout (and outside of) the nervous system. FLNA homodimers regulate the actin cytoskeleton through interactions derived from its multiple receptor binding

Table 1. Human cortical malformation syndromes

Cortical malformation	Gene	Impaired developmental stage				
		Proliferation	Exit from VZ	Migration	Arrest	Regionalization
Microcephaly						
MCP vera	ASPM	+				
MCP vera	Microcephalin	+				
MCP + metabolism	SLC25A19	+				
MCP + immunodeficiency	Nibrin	+				
Periventricular heterotopia						
PH	Filamin		+			
PH + microcephaly	ARFGEF2	+	+			
Classical lissencephaly						
Lis/SBH	DCX			+		
Lis	LIS1	*		+		
Lis + CH	RELN			+	+	
Lis + MCP	ARX	+		+		*
Cobblestone lissencephaly						
FCMD CL + muscle abnormality	Fukutin				+	
MEB CL + muscle-eye abnormality	POMGnT1				+	
Walker Warburg CL + muscle-eye abnormality (severe)	POMT1				+	
Polymicrogyria/pachygyria						
BPP	Unknown			Unknown		
BFPP	Unknown			Unknown		
Focal cortical malformations						
Tuberous sclerosis	TSC1, TSC2	+, +				
Schizencephaly	EMX2					+

*Probable impairment.
BFPP—bilateral frontoparietal polymicrogyria; BPP—bilateral perisylvian polymicrogyria; CH—cerebellar hypoplasia; CL—cobblestone lissencephaly; FCMD—Fukuyama congenital muscular dystrophy; MCP—microcephaly; MEB—muscle-eye-brain disorder; PH—periventricular heterotopia; SBH—subcortical band heterotopia.

regions, including β-integrins, thereby regulating cell stability, protrusion, and motility [18]. Loss of β-integrin–dependent adhesion of neurons onto the radial glia could potentially disrupt neuronal exit from the VZ [19]. Similarly, impaired branching of actin filaments through altered FLNA interactions with other actin-related proteins such as FLNB could destabilize the leading edge of migrating neurons [20]. Overexpression of an FLNA interacting protein (FILIP) in VZ cells has also been shown to cause FLNA degradation and prevent migration from the VZ [21]. Finally, FLNA interacts with two extracellular matrix adhesion-associated proteins, Mig-2 and migfilin. Together, they appear to modulate actin assembly and cell shape, such that disruption in cell shape could impair neurons from exiting the VZ [22•].

Although the formation of PH may imply a failure in departure of neural precursors from the VZ, the addition of microcephaly would also suggest failure in proliferation as well. The autosomal recessive form of PH with microcephaly (ARPHM) results in epilepsy, microcephaly, and severe developmental delay and is caused by mutations in the adenosine diphosphate (ADP)-ribosylation factor guanine exchange factor 2 (ARFGEF2) gene (Sheen and Walsh, unpublished data). ARFGEF2 encodes for brefeldin-inhibited GEF-2 (BIG-2), a 1785-amino acid protein that serves in the exchange of guanine diphosphate (GDP) for guanine triphosphate (GTP) required by the ADP ribosylation proteins (ARP). The ARPs are implicated in intracellular membrane and vesicular trafficking through the trans-Golgi network and appear to be regulated by BIG proteins [23,24]. Inhibition of BIG-2 causes retraction of axonal and dendritic growth cones in vitro [25,26], such that a similar inhibition of attachment of the leading processes in migratory neurons onto radial glia could give rise to PH. Furthermore, disruption in cell cycle during M phase from altered membrane or vesicular trafficking necessary for cell separation may give rise to the clinically evident microcephaly. However, the actual motility of the neurons may remain largely intact as a large proportion of these neurons appear to reach their appropriate laminar position in the cortex. Thus, regulation of vesicular and membrane trafficking by ARFGEF2 at the VZ lumen would be the most parsimonious location, giving rise to both microcephaly and PH, with preservation of neuronal migration and motility.

Classic Lissencephaly (Smooth Brain) Is Caused by Disorders in Neuronal Migration

After postmitotic neurons exit from the ventricular zone, they migrate through the intermediate zone along a radial glia scaffolding into the cortical plate, eventually forming the six layers of the neocortex (Fig. 1B) [27]. A secondary tangential migration by the inhibitory gamma-aminobutyric acid (GABA)-ergic neurons occurs from the adjacent striatum [28]. Extracellular guidance cues, including the Reelin protein secreted from Cajal-Retzius cells of the largely acellular molecular layer next to the pial surface, assist in spatial positioning of the neurons [1]. In general, earlier-born neurons form the deeper cortical layers, whereas later-born neurons form the more superficial layers adjacent to the pial surface. Eventual regional specification presumably gives rise to characteristic sulcal and gyral folds within the human brain.

Disruptions in neuronal migration alter the highly organized architecture of the neocortex, leading to a "smooth" brain (lissencephaly), with loss in sulci and gyri, an abnormally thick cortex (10 to 20 mm compared with 2.5 to 4 mm in the normal cortex), and loss in cortical lamination. As seen with syndromic causes of microcephaly, some causes of lissencephaly are associated with non-CNS findings. For example, impairment in neuronal metabolism can give rise to altered cell migration. Zellweger's syndrome is characterized by various migration abnormalities, including polymicrogyria of the cerebral cortex, pachygyria around the sylvian fissure, and heterotopia. Defects in the mitochondrial desaturation pathway involving docosahexenoic acid result in impaired cellular metabolism and failure in migration [29]. This failure in metabolism, however, can also lead to cardiac, ocular, and gastrointestinal abnormalities.

In contrast to Zellweger's syndrome, most forms of lissencephaly are CNS specific. Classic lissencephaly represents a spectrum of cortical malformations ranging from a simplified cortex to total absence of cortical convolutions (agyria) to broadened gyri (pachygyria). An abnormally thick cortex, heterotopia in the medulla, enlarged ventricles, and midline hypoplasia of the cerebellum may be associated findings in some of the lissencephalic syndromes. Thus far, four loci with corresponding genetic mutations have been identified. X-linked lissencephaly (XLIS) maps to Xq22.3-q23, autosomal dominant Miller-Dieker syndrome (MDS) maps to chromosome 17p13.3, autosomal recessive lissencephaly with cerebellar hypoplasia (LCH) maps to 7q22, and X-linked lissencephaly with abnormal genitalia (XLAG) maps to Xp22.12 (Table 1) [30–32].

Genes that regulate microtubule function not surprisingly appear to influence neuronal migration causing lissencephaly. XLIS is characterized by classic lissencephaly in hemizygous male subjects and a milder phenotype, subcortical band heterotopia (SBH), in heterozygous female subjects. In affected females with SBH, neurons are partially arrested in their migration, residing as a poorly organized band of neurons in the white matter beneath a relatively normal cortex. The phenotypic difference between men and women is likely due to random X inactivation. Affected XLIS male patients share similar clinical features as individuals with classic lissencephaly. In female patients with SBH, the phenotype may be milder, including behavioral problems, epilepsy, and mental retardation. The thickness of the heterotopic band and the degree of pachygyria correlate with the likelihood of developing Lennox-Gastaut syndrome. The XLIS disorder is caused by mutations in doublecortin (DCX). DCX encodes a 40-kD soluble phosphoprotein that causes microtubule polymerization and is coexpressed in neurons with microtubules during periods of neuronal migration [33]. As expression is detected only in migratory neurons of the central and peripheral nervous system and not in neural precursors, XLIS likely represents a "pure" migratory defect.

The most common cause of classic lissencephaly seems to be mutation in a gene encoding another microtubule regulatory protein, LIS1. Over 90% of MDS patients have a mutation in Lissencephaly1 (LIS1), resulting in the characteristically smooth cortex with severe developmental delay and infantile spasms. LIS1 encodes the noncatalytic subunit of platelet activating factor-acetylhydrolase, a heterotrimeric G-protein that inactivates platelet-activating factor (PAF). Although PAF may control the differentiation of neuronal cells, adhesion properties of neural cells, and initiation of migration through changes in calcium fluxes, this contribution to neuronal development is unclear. Rather, as a ubiquitously expressed 45-kD microtuble phosphoprotein, LIS1 binds tubulin and regulates nuclear translocation through interaction with the dynein motor during migration [34]. Recent studies have also demonstrated a direct interaction between DCX and LIS1, consistent with a primary function in microtubule regulation [35•]. The virtually identical lissencephalic picture seen radiographically between heterozygous LIS1 patients and male DCX patients suggests a shared migratory defect. LIS1, however, also interacts with mNUDE and Nudel, which are nuclear distribution genes that are involved in the dynamic reorganization of the microtubule organizing center during cell division [36,37]. Inhibition of Lis1 can also impair cell division through disruption of microtubule function. Whether a shared contribution of a proliferative defect in heterozygous LIS1 patients contributes to these individuals' phenotype remains to be determined.

Although intrinsic failure in neuronal migration through disruption of microtubule function can result in lissencephaly, loss of extrinsic molecular signals and cellular interactions can present with similar cortical migration abnormalities. Autosomal recessive lissencephaly with cerebellar hypoplasia (LCH) is caused by a mutation in reelin (RELN) and is associated with a moderately thickened cortex and pachygyria, abnormal hippocampal formation, and severe cerebellar hypoplasia

with absent folia. Affected individuals with LCH have severe developmental delay, seizures, and hypotonia. RELN, a 388-kD protein containing eight EGF repeats, is secreted by Cajal-Retzius cells of the embryonic preplate, the marginal zone, and the cerebellar external granular layer. The protein presumably acts on migrating neurons through interactions with the very low-density lipoprotein (VLDL) receptor, the apolipoprotein E (apoE) receptor 2, α3β1 integrin, and protocadherins on the neurons. Reln mutant mice, as well as knockout mice lacking the VLDL receptor and apoE receptor 2, share similar features including inversion of cortical layers and absence of cerebellar foliation [32,38]. Thus, loss of extrinsic reelin signaling or the counterpart receptors leads to disruption of neuronal migration and arrest with laminar inversion.

Although perturbed local molecular interactions can impair neuronal migration, disruption of genes that regulate regional specification and development also appears to give rise to lissencephaly. XLAG is caused by mutations in the aristaless-related homeobox gene (ARX) with shared homology to the *Drosophila* a1 gene. Homeobox genes act as transcription factors that direct the coordination of a cascade of genes in control of various aspects of development, including nervous system development. ARX is associated with anterior pachygyria and posterior agyria with a moderately thickened brain cortex (6 to 7 mm), dysplastic basal ganglia, and complete agenesis of the corpus callosum in hemizygous male subjects. The cortex is trilayered, containing exclusively pyramidal neurons, the basal ganglia are disorganized, and the white matter shows gliosis and spongiform changes. Heterozygous female subjects may display agenesis of the corpus callosum. Affected male subjects have intractable epilepsy of neonatal onset, severe hypotonia, and early death, whereas female subjects may have hyperreflexia, mental retardation, and epilepsy. ARX is highly expressed as a 3.3-kb transcript in fetal brain. Expression appears highest in the neural precursors from the germinal matrix of the ganglionic eminence and the ventricular zone of the telencephalon. Arx mutant mice demonstrate reduced brain size secondary to defects in proliferation, loss of region specific markers, and abnormalities in nerve fiber tracts. Aberrant migration of the GABAergic interneurons is also seen in the ganglionic eminence and neocortex [39,40]. The multitude of cortical defects resulting from a mutation in ARX and the presumed function of homeobox genes are consistent with a genetic role in regional specification whereby multiple developmental processes, including neuronal migration and proliferation, are affected.

Cobblestone Lissencephaly Reflects Abnormal Arrest of Neuronal Migration

During development, neurons migrate toward the pial surface and thereby divide the preplate into the marginal zone and subplate. The marginal layer ultimately forms layer 1 of the cortex whereas the subplate becomes layer VIb (Fig. 1B). The relatively sparse marginal layer also contains the reelin-producing Cajal-Retzius cells, which appear to regulate neuronal migration and cortical lamination. However, the layer also serves as a physical barrier preventing migratory neurons from extending past the pial surface [1].

Loss of this structural barrier can result in migration of heterotopic neurons beyond the marginal zone into the leptomeninges and through the external basement membrane during cortical development (termed cobblestone lissencephaly). Disrupted cerebellar architecture, hydrocephalus, and ocular abnormalities including retinal dysplasia can be associated findings in cobblestone lissencephaly [41,42]. Thus far, three autosomal recessive loci have been mapped, with identification of their corresponding genes. Japanese Fukuyama congenital muscle dystrophy (FCMD) maps to chromosome 9q31, Finnish muscle-eye-brain disease (MEB) maps to chromosome 1p32, and Walker Warburg syndrome (WWS) maps, in part, to chromosome 9q34 (Table 1) [43–45].

The shared phenotypes of the various cobblestone lissencephalies are consistent with what is believed to be the known function of the responsible genes involved. All three cobblestone lissencephalies have demonstrated loss in glycosylation of the dystroglycans. FCMD is often caused by a founder mutation with a retrotransposal insertion at the 3′ end of the fukutin gene, which encodes a 461-amino acid protein that shares homology with fringe-like glycosyltransferases. MEB disorder is caused by mutations in protein O-mannose β-1,2-N-acetylglucosaminyltransferase (POMGnT1), which participates in the synthesis of O-mannosyl glycan, a laminin-binding ligand of α-dystroglycan. Mutations in POMGnT1 often result in loss of enzymatic function, causing a selective deficiency in α-dystroglycan. Finally, some cases of WWS are caused by a mutation in O-mannosyltransferase 1 (POMT1). POMT1 catalyzes the first residue (mannose) onto a protein moiety, whereas POMGnT1 in MEB catalyzes the second residue (N-acetylglucosamine) onto the mannose [43–45].

Recent studies suggest that the loss of glycosylation epitopes on α-dystroglycans disrupts the structural integrity of the molecular layer and gives rise to cobblestone lissencephaly. The hypoglycosylation of dystroglycan abolishes binding activity for such ligands as laminin, neurexin, and agrin, and thereby compromises the integrity of the dystrophin-associated extracellular matrix adhesion complex. Thus, post-translational biochemical and functional disruption of α-dystroglycan disrupts the basal lamina and permits the overmigration of neurons through the pial surface [44,45,46•,47•,48]. Whether other targets of these same glycosyltansferases also regulate neuronal migration is unknown.

The varying degrees of severity in cerebral, cerebellar, and ocular malformations provide a means for clinical distinction between the different syndromes. Individuals

with FCMD typically have less severe cobblestone lissencephaly with minor or no eye abnormalities. This relatively less severe phenotype may reflect the more limited expression of fukutin and type of mutation. Individuals with MEB share the characteristic cobblestone complex in addition to ocular abnormalities, but the lissencephaly is largely limited to the occipital lobe. The POMGnT1 mutations in MEB disrupt the second residue of the protein moiety, suggesting a partially intact and functional dystroglycan. Lastly, individuals with WWS are most severely affected with cobblestone lissencephaly, agenesis of the corpus callosum, midline cerebellar hypoplasia, hydrocephaly, and on occasion, an encephalocoele. The worsened severity in WWS as compared with MEB is not surprising given that POMT-1 mutations abolish the first glycosylation residue and likely entirely abolish dystroglycan function.

Disorders of Cortical Organization and Regionalization

Abnormal gyral patterns (pachygyria and polymicrogyria)

Polymicrogyria refers to excessive cortical folding and abnormal cortical layering, which lead to formation of multiple small gyri. Among the several syndromes featuring polymicrogyria, bilateral perisylvian (BPP) and bilateral frontoparietal polymicrogyria (BFPP) clearly have a familial mode of inheritance. Genetic heterogeneity is likely in BPP, including autosomal recessive, X-linked dominant, and X-linked recessive forms of inheritance, and an association with 22q11.2 deletions. BFPP follows an autosomal recessive inheritance and maps to 16q13 [49,50]. The regional differences and complexity of gyral patterns argue that those genes responsible for these cortical malformations will inherently disrupt different regions of the brain at multiple stages of cortical development (Fig. 1B). However, the exact cause of these regional disruptions will not be understood until the appropriate causative genes are identified.

Focal cortical malformations

Genetic syndromes giving rise to focal disorders of cerebral cortical development can reflect a number of different mechanisms. For example, there may be differences in phenotypic penetrance of genes that are widely expressed across the cortex, as well as mutations in genes whose expression pattern or essential functions are relatively region specific. Finally, there are cortical malformations, notably those associated with tuberous sclerosis, that follow the classical Knudson "two hit" model of recessive oncogenes, and hence the second hit occurs stochastically in some, but not all, cortical progenitor cells.

Tuberous sclerosis (TS) represents an inherited autosomal dominant disorder with congenital anomalies in many organ systems. The brain is characterized by cortical "tubers," representing focally dysplastic regions of cortex, and by subependymal nodules that lie next to the ventricular zone and that sometimes transform to cause subependymal giant cell astrocytomas. Affected individuals typically have seizures and developmental delay. TS is caused by mutations in at least two genes, TSC1 and TSC2, on chromosomes 9q34 and 16p13.3, encoding for the protein products hamartin and tuberin, respectively. Both hamartin and tuberin have tumor suppressor function as demonstrated by loss of heterozygosity studies [51]. Inhibition of hamartin disrupts cell adhesion [52], whereas inhibition of tuberin directly inactivates cell cycle inhibitory gene P27kip1 [53]. Both hamartin and tuberin interact to form heterodimers, suggesting that disruption of either protein could lead to a loss of cell cycle inhibition and focal regions of increased proliferation [54].

Schizencephaly refers to a cleft through the cerebral cortex, extending from the lateral ventricles to the pial surface. Although familial occurrence is rare, heterozygous mutations in the EMX2 gene appear to cause schizencephaly, with affected individuals presenting with partial epilepsy. EMX2 is located on chromosome 10q26.1 and represents the mammalian homologue to the *Drosophila* homeotic gene. Expression follows anterior to posterior and medial to lateral gradients, with localization to neuroblasts in the cortical ventricular zone and postmitotic Cajal-Retzius cells. In Emx2 mutant mice, Reelin can be found at the time of cortical preplate formation, but protein expression prematurely declines and disrupts radial glial development, neuronal migration, and cortical plate formation [17]. The absence of EMX2 also shifts cortical regionalization, with anterior and lateral structures predominating over posterior and caudal areas. Such regional differences may give rise to schizencephaly [55–57], but the precise reasons why a gene expressed throughout the cortex gives rise to relatively focal, and frequently unilateral, phenotype is not clear.

Conclusions

Developmental genetic syndromes provide an increasingly expansive overview of genetic function in relationship to human disease. Although the current review summarizes the recently identified genes responsible for the more commonly inherited disorders of cortical development, it is likely that numerous related genes with related functions will comprise many more still undescribed developmental genetic syndromes. Further identification of the genetic basis for these cortical malformations will provide insight into the emerging genetic repertoire required in neural proliferation, neuronal migration, and differentiation.

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