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HUMAN BRAIN MALFORMATIONS AND THEIR LESSONS FOR NEURONAL MIGRATION

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■ **Abstract** The developmental steps required to build a brain have been recognized as a distinctive sequence since the turn of the twentieth century. As marking tools for experimental embryology emerged, the cellular events of cortical histogenesis have been intensively scrutinized. On this rich backdrop, molecular genetics provides the opportunity to play out the molecular programs that orchestrate these cellular events. Genetic studies of human brain malformation have proven a surprising source for finding the molecules that regulate CNS neuronal migration. These studies also serve to relate the significance of genes first identified in murine species to the more complex human brain. The known genetic repertoire that is special to neuronal migration in brain has rapidly expanded over the past five years, making this an appropriate time to take stock of the emerging picture. We do this from the perspective of human brain malformation syndromes, noting both what is now known of their genetic bases and what remains to be discovered.

CORTICAL MALFORMATION: Disorders of Neuronal Position

Clinical syndromes involving cerebral cortical malformation are recognized after the fact by the abnormal position of neural cells. This static picture can only suggest the mechanism by which the disorganized brain developed. The movement of cells from their origins in the ventricular zone may be impaired in a number of ways. Primary neurogenesis or cell number may be altered by disturbed cell proliferation, fate determination, and programmed cell death. The failure of particular cells to differentiate or the improper timing of the birth of a neuron or glial cell may alter the fate and positional information of other cells in the region. The migration of cells from the ventricular zone may be curtailed by interference with the mechanical motors and cytoskeletal dynamics of the cells. Alternatively, the molecular signals

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that initiate movement, guide the cell in its migration, and inform it that the final position has been reached may be altered. Once the position of the cell body is established, assembly and consolidation of neurite/axonal projections and synapses are further established and refined, in part accounting for the survival of neurons and their associated glia.

Much recent interest is trained on the molecules affecting neuronal migration, but their actions may not be purely confined to cell movement. Thus, the events that organize brain structure include neurogenesis, early mid and late migration, as well as axon projection and guidance, all of which are anticipated to overlap considerably. Therefore, the classification of a malformation as a neuronal migration syndrome should be viewed with caution until the function of the responsible gene product is established.

Neuronal Migration Syndromes

The molecular events in neuronal migration are multifaceted and undoubtedly share many features with other migrating cells (for general discussions see Mitchison & Cramer 1996, Condic & Letourneau 1997). However, not all the molecular players in cell motility are equivalent, because there are both human and animal disorders in which migration impairment is virtually restricted to brain. Therefore, superimposed on these basic steps there must be regulatory aspects that are unique to brain. At least four requirements must be fulfilled to move and organize cells in the developing cortex (Figure 1). First, cells must receive signals to "go." Second, adhesive and contractile elements must be coordinately regulated to produce strong adhesion at the leading edge of the cell and weaker adhesion at the rear, ultimately translating into a net movement of the cell when cytoskeletal elements contract. Third, signals must determine the direction or vector of movement. Finally, "stop" signals must inform cells when they have reached their final destination. There are numerous opportunities for genetic mutation to interfere with neuronal migration. Early indications from the reeler and Kallmann syndrome mutations suggested that the unique aspects of neuronal migration in brain would derive from extracellular matrix molecules having selective expression in brain. The astonishing insight from human mutations is that the intracellular cytoskeletal machinery of migrating neurons has distinctive character as well.

To date, over a dozen molecules that are peculiar to neuronal migration in brain have been reported (Table 1). At least half were identified first from clinical human studies. The rest were discovered either in mice or in *Drosophila* (the relevance of the latter for mammalian development subsequently being confirmed in mouse). The cellular events and many of the molecular components of neuronal migration have recently been extensively reviewed in this series and are not repeated here (Hatten 1999). Instead, brain formation is discussed in view of human clinical syndromes recently shown to arise from impairment of neuronal migration. Additional syndromes thought to represent migration abnormalities, but for which genetic identification is currently lacking, are pointed out. These provide

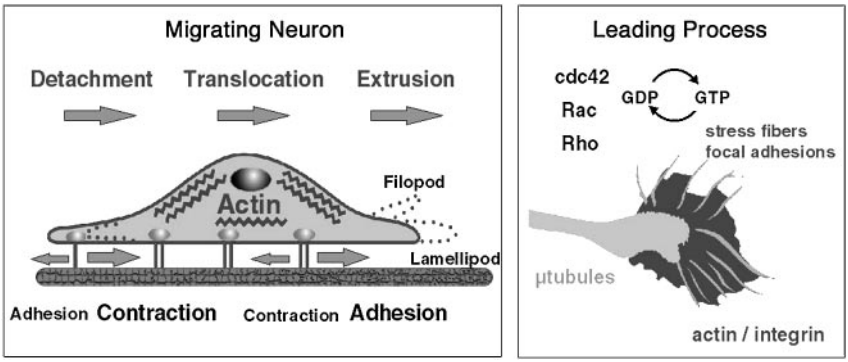

Figure 1 Molecular events in neuronal migration. The left panel summarizes the subcellular components of migration. The right panel further illustrates events at the leading process.

opportunities to uncover new pieces to the puzzle. By far the largest class of neuronal migration syndromes are the lissencephalies (from "lissos," smooth + "encephaly," brain) and are dealt with first.

The Lissencephalies

Cortical malformation often has severe consequences in humans, including mental retardation, epilepsy, paralysis and blindness. Less severe deficits occur when only selected regions of cortex or only a portion of the cortical cell population are affected. High resolution imaging has brought the realization that displaced neurons, or heterotopia, are more prevalent than once thought and that up to 25% of childhood epilepsy is associated with heterotopia (Kuzniecky et al 1993). Neuronal heterotopia are often thought to arise from interference in neuronal migration mechanisms during brain development. Among malformations with heterotopia, the lissencephalies have been grouped because of their probable shared mechanism of incomplete neuronal migration from the ventricular neuroepithelium (Barkovich et al 1996, Dobyns in press). Although these malformations have distinctive features on magnetic resonance imaging, they share a loss of normal sulcation and gyral formation, as well as thickening of the cortical gray matter.

Classical Lissencephaly This term is used to encompass a spectrum of simplified cortex ranging from total absence of cortical convolutions (agyria) to broadened gyri (pachygyria) with abnormally thick cortex (typically 10–20 mm compared with 2.5–4 mm in the normal cortex) (Dobyns & Truwit 1995, Dobyns et al 1996a). This spectrum intersects with double cortex (DC, aka subcortical band heterotopia or SBH), in which neurons are partially hung up in their migrations, finally to reside as a poorly organized band of neurons in the white matter beneath a relatively normal cortex. Associated abnormalities can include enlarged lateral

TABLE 1 Summary of genes affecting neuronal migration in the central nervous system

Migration Molecule[a]	Gene	Mutation phenotype		References
		Murine	Human	
Platelet activating factor Acetylhydrolase 1b1 (Pafah1b1) (signaling/tubulin cytoskeletal dynamics)	*LIS1*	Lis1−/+ animals with neuronal migration delay	Miller Dieker syndrome (MDS) Lissencephaly (ILS)[b] (class LISa1-4) LIS with cerebellar hypoplasia (LCH) (class LCHa)	Reiner et al 1993 LoNigro et al 1997 Hirotsune et al 1998 Ross et al 2001
Doublecortin (Dbcn) (microtubule associated protein-cytoskeletal dynamics)	*DCX/XLIS*		Double cortex (DC) or (SBH) subcortical band heterotopia X-linked LIS (XLIS) (class LISb1-4) LCH (class LCHa)	Gleeson et al 1998 Des Portes et al 1998 Pilz et al 1998 Ross et al 2001
Reelin [extracellular matrix (ECM) molecule]	*RELN*	Reeler: inverted cortex with layer 5 neurons superficial, failure of preplate to split	LCH (class LCHb)	Caviness 1977 D'Arcangelo et al 1995 Sheppard et al 1997 Hong et al 2000
Disabled (docking protein for cAbl tyrosine kinase, intracellular signaling)	*DAB*	Scrambler/yotari (phenotype identical to reeler)	LCH? (predicted, based on similarity of reeler and scrambler mice)	Sheldon et al 1997 Ware et al 1997
VLDLR, ApoER2 (lipoprotein receptors that also bind reelin)	*VLDLR* *ApoER2*	Knockouts with reeler-like cortex		Heisberger et al 1999 Trommsdorff et al 1999 D'Arcangelo et al 1999

Cdk5 (neurofilament phosphorylation)	*CDK5*	Knockout with reeler-like cortex		Gilmore et al 1998
p35 (activating subunit of cdk5)	*p35*	Knockout similar but less severe than *Cdk5*−/− nulls		Chae et al 1997 Kwon & Tsai 1998
Peroxisomal proteins	*PEX2* *Pxr1*	Deficient mice display heterotopia similar to Zellweger patients	Zellweger syndrome	Faust & Hatten 1997 Baes et al 1997
Filamin-1 (actin crosslinking phospoprotein)	*FLN1*		Bilateral periventricular nodular heterotopia (BPNH), neurons fail to leave the VZ	Fox et al 1998
Fukutin (putative ECM protein)	*FCMD*		Fukuyama congenital muscular dystrophy (FCMD)-cobblestone complex type II LIS & myopathy	Kobayashi et al 1998
Anosmin-1 (ECM protein)	*KAL1*		Kallmann syndrome	Hardelin et al 1992 Soussi-Vanicostas et al 1998
Astrotactin 1 (neuronal surface molecule)	*ASTN1*	Nulls with neuronal migration delay in cerebellum and cortex		Adams et al 2001

[a]Suspected role appears in parentheses.

[b]ILS = isolated lissencephaly sequence. Refers to classical LIS without the facial features of MDS.

ventricles, hypoplasia of the corpus callosum, and hypoplasia of the cerebellum, typically in the midline. Two genes, *LIS1* and *DCX*, account for the majority of classical *lissencephaly* (LIS) (Pilz et al 1998). Genotype-phenotype analyses have revealed a gradient of LIS severity that characterizes *LIS1* (posterior worse than anterior, P>A) or *DCX* (A>P) mutations, from which a detailed grading system has been developed (Dobyns et al 1999b, Dobyns in press). Such classification has proven useful in clinical diagnosis and helpful in recognizing causes of LIS and DC/SBH. In addition, despite the striking similarity of LIS caused by *LIS1* or *DCX*, the distinct gradient suggests that these genes may participate in separate though related molecular pathways (Pilz et al 1998).

Chromosome 17-Linked Lissencephaly (LIS1 Gene) The first LIS syndrome delineated is Miller-Dieker syndrome, which is manifested by severe LIS and characteristic facial abnormalities (Dobyns et al 1993). Chromosomal analysis shows visible deletions of 17p13.3 in over 90% of Miller-Dieker syndrome patients, suggesting that this is a contiguous gene deletion syndrome in which the characteristic facial features are caused by involvement of loci neighboring *LIS1*. Isolated lissencephaly sequence (ILS) consists of classical LIS with relatively normal facial appearance. Fluorescence in situ hybridization (FISH) studies show deletions of 17p13.3 in about 40% of ILS children (Dobyns et al 1994). Extensive genotype-phenotype correlation reveals that mutations in the *LIS1* gene together with *DCX* (see below) account for 76% of classical LIS (Pilz et al 1998). Therefore, as much as 24% of ILS cases could involve another gene. The *LIS1* gene has been cloned and confirmed by identification of *LIS1* point mutations and intragenic deletion in patients with ILS (Lo Nigro et al 1997, Reiner et al 1993).

Gene dosage of *Lis1* has been examined in mice (Hirotsune et al 1998). The null state produces early embryonic lethality in mouse, which may explain why recessive inheritance of *Lis1* mutation has not been observed in humans. Mice heterozygous for *Lis1* survive and reveal abnormalities primarily in cerebral cortex, but also hippocampus and cerebellum, owing to the impaired, slower migration of neurons (Hirotsune et al 1998, Clark et al submitted). Interestingly, though these mice reveal migration defects, the malformation is distinct from the prototype neuronal migration mouse model, *reeler* (see below), in that *Lis1*+/− cortex is not inverted and the hippocampus and cerebellum are far less involved.

LIS1 encodes a noncatalytic subunit of platelet activating factor-acetylhydrolase, or Pafah1b1, and is part of a G-protein-like ($\alpha 1/\alpha 2$)ß trimer (Ho et al 1997). Hereafter, this subunit is referred to as Lis1 protein. Pafah is known to regulate platelet activating factor (PAF), a potent lipid first messenger that is involved in processes ranging from general cell activation to inflammatory and allergic reactions to carcinogenesis and apoptosis. It is not yet proven whether Lis1 exerts its influence on migration through regulation of PAF. However, in vitro studies of neuronal cell motility by Clark and colleagues have shown that exposure to excess PAF inhibits unidirectional cerebellar granule cell movement in culture along neighboring axons (Bix & Clark 1998). Thus, at least one of the roles of Lis1

protein in neuronal migration may be through regulation of PAF. Interestingly, this factor may be involved in another neuronal migration disorder, Zellweger syndrome, in which mutant peroxisomal proteins are expected to result in elevated PAF levels (see below; Faust & Hatten 1997).

Lis1 is a soluble protein with seven WD40 repeats forming a seven-bladed propeller-like structure involved in protein-protein interactions (Garcia-Higuera et al 1996). Lis1 binds tubulin and reduces microtubule catastrophe in vitro, suggesting that it may stabilize the microtubule cytoskeleton (Sapir et al 1997, 1999). Significantly, Lis1 is a highly conserved homologue of the NUDF protein in Aspergillus, in which it is required for nuclear translocation through interaction with a dynein motor (Xiang et al 1995). In fungus, NUDF interacts with several proteins including NUDC and NUDE to regulate this translocation (Chiu et al 1997, Efimov & Morris 2000). Recently, Lis1, overexpressed in mammalian cells and neurons, has been shown to bind cytoplasmic dynein and to affect microtubule organization (Feng et al 2000, Sasaki et al 2000, Smith et al 2000). In this model Lis1 promotes the peripheral, plus end–directed movement of microtubule segments by dynein motors that are attached to stable microtubules, oriented with minus ends anchored at the centrosome and plus ends at the peripheral membrane skeleton. In conditions of low Lis1 levels dynein motor activity is reduced and microtubule segments accumulate near the nucleus. One of the challenges to understanding Lis1 function is that Pafah is a ubiquitously expressed enzyme, yet loss of a single *Lis1* allele produces defects largely confined to brain. Based on Western analysis, Tsai and colleagues hypothesized that the neuronal specificity of *Lis1* haploinsufficiency relates to the unusually high levels of Lis1 expressed in wild type neurons (Smith et al 2000).

X-Linked Lissencephaly (DCX/XLIS Gene) XLIS refers to the syndrome of classical LIS in hemizygous males and DC/SBH in heterozygous females. The clinical features and responsible gene were delineated only recently (Dobyns et al 1996a, Ross et al 1997, Gleeson et al 1998, des Portes et al 1998). The clinical manifestations of XLIS in males are very similar to those of chromosome 17 associated ILS. DC/SBH is characterized by a symmetric and circumferential band of gray matter, located just beneath the cortex and separated from it by a thin band of white matter. The phenotype arises because females, though they have two X-chromosomes, inactivate one early in embryogenesis through the process of random X-inactivation. This process ensures that on average, half of the cortical neurons in an affected female will inactivate the mutant *DCX* allele and express normal protein, whereas the other half will inactivate the normal allele and become impaired in their migration, to form the band heterotopia. Skewing of X-inactivation can lead to the most severe form of lissencephaly in a *DCX* female (Ross et al 1997). DC/SBH individuals are far less affected than classical LIS patients and may manifest seizures with cognitive impairment of varying severity. Indeed, ~25% of DC/SBH patients possess normal or near normal intelligence (Dobyns et al 1996a). The degree of neurologic impairment roughly coincides

with the thickness and extent of the subcortical band, which is presumed to arise from the incomplete migration of affected cells to the forming cortical gray matter (cortical plate). *DCX* accounts for ~85% of sporadic DC/SBH and 100% (11 of 11) of X-linked, DC/SBH pedigrees (Gleeson et al 1999b, Matsumoto et al 2000). Both LIS and DC/SBH due to mutations in *DCX* reveal an anterior (A>P) gradient that has been helpful in recognizing mutational heterogeneity in the gene that produces milder forms of the disorder (Gleeson et al 1999b, Matsumoto et al 2000).

The XLIS gene, *DCX*, encodes a 40 kD soluble protein named doublecortin (Dbcn) (Gleeson et al 1998, des Portes et al 1998). Unlike the ubiquitously expressed Lis1 protein, Dbcn has been detected only in neurons of the central and peripheral nervous system (Gleeson et al 1999a). The protein bears homology to the noncatalytic portion of the CAM-kinase member, DCAMKL1. Dbcn displays several structural features of interest, including a predicted motif for phosphorylation by members of the cAbl, nonreceptor tyrosine kinase family (Gleeson et al 1998). This is likely to be significant, because another neuronal migration disorder in the scrambler mouse is associated with mutation in *disabled* (*mDab*), whose gene product in *Drosophila* is a regulatory protein for cAbl (Ware et al 1997, Sheldon et al 1997). Extensive genotype-phenotype analysis of patient populations has revealed two internal repeat regions in Dbcn that are essential for its function (Gleeson et al 1999b, Matsumoto et al 2000). Mutation analysis in vitro and in situ indicates that these repeats bind to tubulin to promote precipitation and stabilization of microtubules (Gleeson et al 1999a, Taylor et al 2000, Horesh et al 1999).

LIS1 and DCX Gene Functions in Neuronal Migration A rough schematic of the emerging relationships among these two genes and other molecules identified in mouse is provided in Figure 2. This is by no means intended to be complete, and several of the assignments are tentative. Nevertheless, the diagram provides a framework in which to consider possible mechanistic relationships. Molecules are viewed at the interface of the actin-based and microtubule-based cytoskeleton. Those depicted have been identified or implicated in neuronal migration (Lis1, Dbcn, cdk5, mDab, reelin, integrins, VLDL and ApoE receptors, Dynein motors, Rac, Rho, cdc42). Included are molecules either shown to interact with these components, or that are closely related and are demonstrated participants in axon extension [enabled (Ena), profilin, cAbl, abl related gene (Arg), Pak1].

To date, the Lis1 and Dbcn proteins have been implicated in regulation of microtubule dynamics by virtue of binding tubulin and reducing microtubule catastrophe (Sapir et al 1997, 1999; Gleeson et al 1999b; Taylor et al 2000). In addition, Clark and colleagues have demonstrated in a yeast two-hybrid system that point mutations found in ILS patients interfere with the association of Lis1 for the 29 and 30 kD subunits of Pafah (Sweeney et al 2000). The fact that all patient mutations in Lis1 examined in this system interfere with binding to Lis1 suggests that the heterotrimeric Pafah complex may be involved in regulating migration. Further

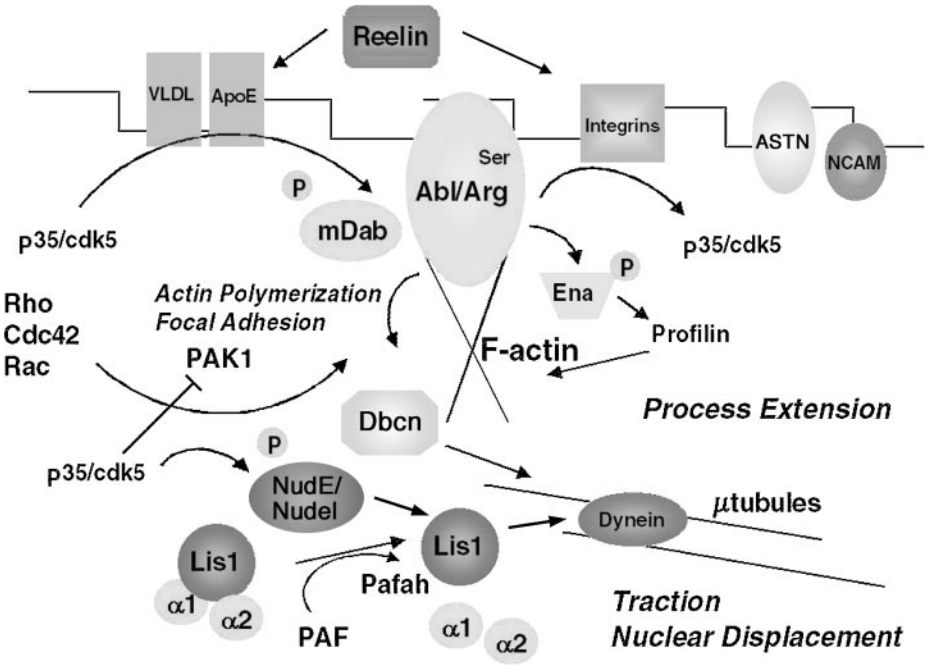

Figure 2 Interrelationships among proteins governing neuronal migration and process extension. Although several assignments are tentative, the diagram provides a framework in which to consider mechanistic interactions. Proteins depicted have been identified or implicated in neuronal migration (Lis1, Dbcn, cdk5, mDab, reelin, integrins, VLDL and ApoE receptors, dynein moters, Rac, Rho, cdc42, ASTN, NCAM). Included are proteins either shown to interact with these components (NudE, Nudel) or that are closely related participants in axon extension [enabled (Ena), profilin, cAbl, abl related gene (Arg), Pak1].

evidence indicates that PAF interferes with binding of Lis1 to the 30 kD subunit and that PAF rescues the migration phenotype of Lis1 haploinsufficient neurons. This suggests a model in which the role of PAF is to mobilize the Lis1 protein from Pafah to exert a downstream effect on migration. In such a model, PAF could rescue neurons expressing low levels of Lis1 by displacing more of Lis1 protein from the complex (GD Clark, GJ Bix, A Shinoya, S Hirotsune, ME Ross et al 2001, submitted for publication).

The downstream, non-Pafah-dependent effects of Lis1 involve additional protein-protein interactions. For example, several recent reports have described a Lis1 interaction with dynein heavy chain that recapitulates the interaction of the homologous proteins demonstrated in Aspergillus (Faukner et al 2000, Liu et al 2000, Smith et al 2000). In addition, interactions have been identified in yeast two-hybrid screens between Lis1 and two homologues of the Aspergillus *NUDE* gene, *mNudE* and *Nudel* (Efimov & Morris 2000, Feng et al 2000, Niethammer

et al 2000, Sasaki et al 2000). In young mammalian neurons, mNudE and Nudel are both co-localized with Lis1 at the microtubule organizing center (centrosome). Not only does mNudE localize to the centrosome, but it simultaneously binds multiple components there that appear to determine the organization of the centrosome (Feng et al 2000). Evidence that this interaction with Lis1 is functionally important comes from the findings that (*a*) missense *Lis1* mutations block mNudE/Lis1 binding, and (*b*) disrupting the interaction of mNudE with Lis1 in *Xenopus* disrupts the lamination of the anterior nervous system (Feng et al 2000). As the cell matures, Nudel/Lis1 distribute into the axon (Sasaki et al 2000). In addition, Nudel is a substrate for phosphorylation by cdk5, an important molecule for process extension and axon fasciculation (Niethammer et al 2000, Sasaki et al 2000). Together, the mammalian data suggest a mechanism in which Lis1 participates in the organization of the microtubule-based cytoskeleton needed for neurite extension and nuclear translocation.

The relationship(s) between Lis1 or Dbcn and other migration molecules in the neuronal migration scheme are tenuous at best. Dbcn has a putative link to the cAbl family of nonreceptor tyrosine kinases through a motif that, based on sequence, should be phosphorylated by an Abl-like kinase (Gleeson et al 1998). The connection between cAbl and neuronal migration is further implicated by observations that (*a*) cAbl mutants in *Drosophila* have an axonal projection and fasciculation defect (Gertler et al 1989, Bashaw et al 2000) and (*b*) mutation in the mouse disabled (*mDab*) gene, which encodes a docking protein for Abl in the fly, produces a reeler-like phenotype (Howell et al 1997, Ware et al 1997). Moreover, binding of the reelin protein to the VLDL or ApoE2 receptor leads to phosphorylation of mDab (D'Arcangelo et al 1999, Hiesberger et al 1999, Trommsdorff et al 1999). Biochemical evidence points to JNK-interacting proteins 1 and 2 as intracellular effector molecules downstream of reelin-ApoER2 interactions (Stockinger et al 2000). This may occur via the nonreceptor tyrosine kinase Fyn, a member of the cAbl family that is known to bind to the intracellular domain of ApoER2.

The functional involvement of the Abl family kinases in neuronal movement is further supported by the demonstration that p35/cdk5, whose loss of function leads to cortical neuronal migration defects, is phosphorylated by cAbl (Chae et al 1997, Kwon & Tsai 1998, Gilmore et al 1998, Zukerberg et al 2000). cAbl in the cytoplasm has itself been demonstrated to bind filamentous actin (McWhirter & Wang 1993), and one of its binding proteins, enabled (Mena in mammals), is known to interact with profilin, a modulator of actin polymerization (Lanier et al 1999). Phosphorylation by p35/cdk5 is further implicated in actin dynamics because the p35 subunit has been demonstrated to interact directly with the small GTPase Rac, and p35/cdk5 hyperphosphorylation of Pak1 inhibits the Pak1 kinase, a modulator of actin polymerization (Nikolic et al 1998).

Additional neuronal migration signaling cascades from the membrane surface that involve adhesion molecules may indirectly impact cAbl-family kinases. For example, another twist to the story of reelin action is the identification of its binding to $\alpha 3\beta 1$ integrin to provide an inhibitory signal to migrating neurons

(Dulabon et al 2000). The downstream events following integrin binding have yet to be clarified, but mice lacking $\alpha 3\beta 1$ integrin express reduced levels of mDab, implicating transcriptional regulation (Dulabon et al 2000). Coming full-circle then, the demonstrated ability of Dbcn to interact with microtubules and its structural motif that suggests phosphorylation by cAbl, a kinase involved in actin cytoskeletal dynamics, position Dbcn protein as a candidate molecule for crosstalk between the actin- and microtubule-based cytoskeleton. Similarly, the multiple substrates emerging for cdk5 implicate this kinase in such a coordinating role.

Lissencephaly with Cerebellar Hypoplasia

This group is only now evolving a nomenclature and comprises six broad classes, lissencephaly with cerebellar hypoplasia (LCH)a–f, that are grouped according to distinguishing features (Ross et al 2001). Within these broader groups, three causative genes have been identified and another locus described. Syndromes of LCH have in common a lissencephaly spectrum of agyria-pachygyria, with mildly (5–10 mm) or markedly (10–20 mm) thickened gray matter. Cerebellar involvement detected by magnetic resonance imaging may be mild, with predominantly midline hypoplasia seen with *LIS1* or *DCX* mutations (LCHa) to severe cerebellar defects with hypoplasia of the cerebellar hemispheres and abnormal or absent foliation (LCHb or d) (al Shahwan et al 1995, Kato et al 1999, Ross et al 2001). Another form of LCH (LCHe) is characterized by an abrupt transition from agyria frontally to gyral simplification of parietal-occipital cortex, associated with moderate cerebellar hypoplasia. A striking phenotypic manifestation (LCHf) is total absence of the corpus callosum. The rarity and lack of families with multiple affected individuals suggests that many of the LCH phenotypes are likely to arise from autosomal recessive mutations.

Recently, mutation has been identified in the human *reelin* (*RELN*) gene that produces LCHb. This distinctive pattern possesses a moderately thickened cortex and pachygyria, markedly abnormal hippocampal formation, and severe cerebellar hypoplasia with absent folia (Hourihane et al 1993, Hong et al 2000). This is of particular interest because the reeler mouse was first proposed as an animal model of lissencephaly in the 1970s, though direct evidence has been lacking (Caviness 1977). *RELN* encodes a large 388 kD protein containing 8 EGF repeats and is secreted by the Cajal-Retzius cells of the embryonic preplate, the marginal zone, the cerebellar EGL, and pioneering cells of the hippocampus (D'Arcangelo et al 1995, Schiffmann et al 1997, Sheppard & Pearlman 1997). One of the receptor types for the Reln protein is the lipoprotein receptors VLDLR and ApoER2 (D'Arcangelo et al 1999). Reln has been recently demonstrated to direct phosphorylation of the mDab1 protein via action of ApoE receptor 2 (Hiesberger et al 1999). The fact that mutation in *Dab1* produces the scrambler mouse, with a brain phenotype nearly identical to the reeler mouse, further implicates mDab1 as an effector of neuronal migration that functions downstream of Reln (Ware et al 1997, Sheldon et al 1997,

Rice et al 1998). However, whether human *DAB1* mutations cause clinical LCH is not yet known.

Additional candidate genes for LCH include segmentation genes, growth and trophic factors identified as important for dorsal-ventral patterning of hindbrain (for summary see Millen et al 1999). One appealing LCH candidate is the neuronal migration gene, astrotactin (*ASTN1*), which was originally identified through investigation of migration-blocking antibodies generated from cerebellar tissues (Edmondson et al 1988). A mouse model lacking *Astn1* reveals reduced volumes of cerebral cortex and cerebellum and subtle disorganization of these structures (Adams N, Dietz G, Kon N, Hatten ME 2001, submitted for publication). Astn1 is a transmembrane protein with fibronectin type III repeats in the extracellular domain (Zheng et al 1996). Expressed on cerebellar granule neurons, Astn1 is required for glia-guided migration of granule cells in culture (Fishell & Hatten 1991, Zheng et al 1996). Astn1 mRNA is also expressed in cerebral cortex and hippocampus. The previous observation of much milder phenotype in *Lis1* knockout mice compared with the human presentation suggests that the clinical syndrome associated with *ASTN1* mutation would likely be more severe than in the mouse.

Cobblestone Complex (Lissencephaly)

Pathologically, cobblestone complex consists of migration of heterotopic young neurons beyond the marginal zone—future layer I—into the leptomeninges through gaps in the external basement membrane. This could result from alteration in the extracellular matrix, a hypothesis that may be supported by the identification of fukutin in *Fukuyama congenital muscular dystrophy* (see below). The movement of neurons into the leptomeninges can obliterate the subarachnoid space and give rise to communicating hydrocephalus or ventricular enlargement owing to impaired reabsorption of cerebrospinal fluid (Gelot et al 1995, Bornemann et al 1997). On first glance, the magnetic resonance imaging features of cobblestone lissencephaly may be difficult to distinguish from those of polymicrogyria. There is a thickened cortical gray matter with a knobby cobblestone surface and few or absent true sulci. Some areas appear as pachygyria with smooth surface. Bands of "white matter" that are composed of glial-fibrous tissue interrupt the gray matter. There are often small cerebellar cysts and white matter neuronal heterotopia. Hydrocephalus may be present and when severe, produces marked thinning of the cortex.

Fukuyama Congenital Muscular Dystrophy (FCMD) This is the second most common form of inherited congenital muscular dystrophy in the Japanese. There is progressive facial and limb weakness with delayed motor development, congenital and progressive joint contractures and elevated serum muscle enzymes (CK-creatine kinase) reaching 10–50 times normal (Fukuyama et al 1981). Brain involvement includes cobblestone complex that is less severe than Walker Warburg syndrome or muscle-eye-brain disease, with minor or no eye abnormalities. There may be mild cerebellar foliation defects, but there is not usually hypoplasia (Aida

et al 1996). This autosomal recessive mutation is the first human syndrome documented to arise from a retrotransposal insertion that interrupts the 3′ end of the transcript on chromosome 9q31-32 (Kobayashi et al 1998). There is a strong founder effect, because 87% of FCMD has been found to carry this mutation and it is rarely encountered outside of Japan or Korea (Toda et al 2000). The gene, *FCMD*, encodes a putative extracellular matrix molecule, called fukutin (Kobayashi et al 1998).

Walker-Warburg Syndrome (WWS) Characteristic features of WWS include severe cobblestone complex and retinal and other eye abnormalities, as well as congenital muscular dystrophy (Dobyns et al 1989, Chadani et al 2000). This is an autosomal recessive disorder that is genetically distinct from FCMD, though severely affected FCMD children may resemble WWS (Chadani et al 2000). The cortex is thickened (7–10 mm), except when it is thinned owing to increased pressure within the cranium from hydrocehpalus, with a mixture of cobblestone complex with diffuse agyria. There are diffuse white matter changes, and irregular laminar heterotopia may appear beneath the cortex. The brainstem is hypoplastic, and there is significant midline>hemisphere cerebellar hypoplasia. Many WWS patients have a retrocerebellar cyst (Dandy-Walker malformation). In some this cyst may protrude through a small defect in the skull, producing an occipital cephalocoele. Eye involvement includes retinal nonattachment or detachment or more mild retinal and optic nerve hypoplasia (Gerding et al 1993). Some have microphthalmia, buphthalmos, colobomas, or high myopia.

Muscle-Eye-Brain Disease (MEB) The MEB gene has been mapped in a Finnish population to chromosome 1p34-p32 (Cormand et al 1999). In the same population children with WWS have been genetically excluded from the 1p34-32 locus of *MEB* or the 9q31-q33 position of *FCMD* (Ranta et al 1995, Cormand et al 2001). MEB consists of cobblestone complex, retinal and other eye abnormalities including a glial preretinal membrane, and myopathy (Haltia et al 1997). Retinal physiological abnormalities may be detected after 1 year of age on electroretinograms or visual evoked potentials. The cortex shows frontal pachygyria and less severe gyral abnormalities in the occipital region. The cerebellum is less involved than in WWS, and the midline may be hypoplastic, but hemispheres are usually normal. Dandy-Walker malformation and cephaloceles are not seen in MEB.

Cobblestone Complex Only Patients with the appearance of cobblestone complex but without significant retinal or muscle pathology have been identified (Dobyns et al 1996b). These three patients from two consanguinous families have been excluded by linkage analysis from the 9q31 locus of *FCMD* and the 1p34 locus of *MEB*. The brain malformation may be diffuse and resemble polymicrogyria, or similar to that in MEB with an A>P gradient. The brainstem and cerebellar vermis in *cobblestone complex only* are mildly reduced in volume, whereas the

cerebellar hemispheres appear normal on magnetic resonance imaging. As in other cobblestone syndromes, cerebellar microcysts may be present.

Other Disorders of Neuronal Migration

Several other disorders, though not associated with a "smooth brain," are nevertheless associated with altered migration of selected subpopulations of neurons.

Bilateral Periventricular Nodular Heterotopia (BPNH or PH) This is characterized by neuronal heterotopia lining the lateral ventricles. Several BPNH families have demonstrated affected women with periventricular nodules, seizures, and normal intelligence (Kamuro & Tenokuchi 1993, Huttenlocher et al 1994). The familial syndrome shows a female predominance and is usually lethal in males, consistent with an X-linked inheritance, though a few severely affected males have been known to survive (Fink et al 1997). On tissue examination, the periventricular nodules contain well-differentiated cortical neurons in the subependymal zone (Eksioglu et al 1996). Like the situation in SBH/DC, the milder phenotype in females is attributed to X-inactivation, with the heterotopic neurons representing cells in which the normal allele is silent. The gene defect in BPNH has been identified as a mutation in *filamin 1* (*FLN1*), encoding a 280 kD actin-crosslinking phosphoprotein (ABP-280) (Fox et al 1998). Fln1 was first identified in white blood cells, where it is required for migration, formation of filopodia, chemotaxis, cell morphology, and platelet aggregation. Fln1 is thought to transduce ligand-receptor binding into actin remodeling necessary for motility. The identification of sporadic cases of periventricular heterotopia affecting females and males equally, suggests that additional autosomal genes, and/or X-linked genes other than *FLN1*, must exist whose function is required to initiate migration from the ventricular region (Raymond et al 1994, Guerrini & Dobyns 1998; ME Ross & CA Walsh, personal observations).

Zellweger Syndrome This syndrome is recognized by a cortical dysplasia resembling polymicrogyria of cerebral and cerebellar cortex, sometimes with pachygyria around the sylvian fissure, and focal subcortical and subependymal heterotopia. There may be subependymal cysts and hypoplasia of the inferior olivary nucleus (Takashima et al 1992). In postmortem cortex there is an increase in cholesterol-ester very-long-chain fatty acids and decreased plasmalogens (Powers & Moser 1998). Thought to arise from errors of peroxisomal metabolic function, the primary abnormality proposed in Zellweger syndrome is a defect in the mitochondrial desaturation pathway–metabolizing Docosahexenoic (22:6n-3) acids (Infante & Huszagh 1997). Several animal models of Zellweger syndrome have been produced. Inactivation of *Pxr1*, encoding the transport receptor for peroxisomal matrix proteins, produces multiple neuronal heterotopia (Baes et al 1997). Similarly, loss-of-function mutation of Pex2, a peroxisome assembly protein, disrupts neuronal migration in mouse brain (Faust & Hatten 1997). Interestingly, such peroxisomal disorders associated with this dysplastic syndrome would be expected to alter

platelet activating factor (PAF) levels in brain, perhaps hinting at a role for this potent first messenger in both classical lissencephaly (*LIS1* mutation) and Zellweger neuronal migration defects.

Kallmann Syndrome The constellation of anosmia due to lack of olfactory bulb development, mental retardation, and hypogonadism comprises Kallmann syndrome. This was recognized early on as a failure of migration of particular neurons of the olfactory cortex and GnRH-secreting cells of the hypothalamus. Autosomal dominant, recessive, and X-linked inheritance patterns have all been described. The X-linked form is associated with mutation in *KAL1*, encoding anosmin-1, a secreted extracellular matrix protein with fibronectin type III–like domains (Hardelin et al 1992, del Castillo et al 1992, Soussi-Yanicostas et al 1998). Adhesion to anosmin-1 depends upon the presence of chondroitin sulfate and glycosaminoglycans on the cell surface. Anosmin-1 has been shown in vitro to modulate neurite outgrowth and fasciculation in a cell type–specific manner (Soussi-Yanicostas et al 1998, Hardelin et al 1999).

Disorders of Axonal Projection and Assembly

These disorders, though rarely identified in a pure form, are closely related to the neuronal migration genes noted above (Table 2). In fact, several migration genes are listed in both Tables 1 and 2 because their roles in neuronal migration and neurite extension have been examined in some detail.

Agenesis of the Corpus Callosum (ACC) Perhaps the most striking examples of defective neurite outgrowth in humans are associated with failure of cortical axons to cross the midline, thereby producing absence or agenesis of the corpus callosum. ACC is found in an impressive array of cortical dysplasia, making it likely to arise from a number of gene defects. Yet when present, ACC speaks to the importance of the involved gene in neurite outgrowth and thus is a valuable clue to the selection of candidate genes. For example, although there may be thinning or partial agenesis of the corpus callosum in ILS/Miller-Deiker or XLIS, total ACC has not been seen in patients with the associated known mutations. ACC is a prominent feature of the CRASH (callosal agenesis, retardation, abducted thumbs, spastic paraparesis, and hydrocephalus) syndrome that has been associated with mutations in the L1 (L1CAM) neuronal adhesion molecule (Sztriha et al 2000). Moreover, a probable X-linked syndrome has recently been identified in five children with LIS associated with ACC and ambiguous genitalia (XLAG), without mutation in either *LIS1* or *DCX* genes (Dobyns et al 1999a). There are numerous examples of human brain maldevelopment associated with ACC, and the reader is referred to several excellent discussions (Marszal et al 2000, Dobyns 1996).

Candidate Genes for Defects in Neuritogenesis and Axon Pathfinding A number of genes implicated in neuronal migration disorders have been observed to

TABLE 2 Summary of genes affecting neurite outgrowth in central nervous system

Nutrition Outgrowth[a]	Gene	Mutation phenotype		References
		Murine	Human	
Mammalian enabled (Mena) (actin reorganization/adhesion)	*MENA*	Marked axonal projection defects in −/− Exacerbated by loss of profilin 1		Lanier et al 1999
Ableson (phosphorylates cdk5)	*cABL*	Nulls are early postnatal lethals		Zukerberg et al 2000
Abl Related Gene (tyrosine kinase regulates actin cytoskeleton)	*ARG*	Enriched in CNS, colocalizes with cAbl/F actin Neural tube defect in double Abl/Arg nulls		Koleske et al 1998
Profilin (binds Mena and regulates actin polymerization)	*Profilin I* *Profilin II*	[b]*Chickadee* mutation in *Drosophila* identical to growth cone arrest of cAbl nulls		Suetsugu et al 1998 Wills et al 1999
Slit (ligand of Robo, repels midline axons)	*slit 1* *slit 2*	Axon outgrowth from retinal explants inhibited by *Slit 2* transfected cells		Rothberg et al 1990 Ringstedt et al 2000

Roundabout (repulsive axon guidance receptor)	*Robo*	[b]Slit/robo interactions first identified in flies; *Drosophila*. Slit repels spinal motor axons in culture		Brose et al 1999 Bashaw et al 2000
Cdk5 (modulates actin dynamics via Rac GTPase and Pak1)	*CDK5*	p35/cdk5 localized to growth cones; mutant forms inhibit neurites		Nikolic et al 1996 Nikolic et al 1998
p35 (activating subunit of cdk5)	*p35*	p35 nulls reveal callosal axon guidance defects		Kwon et al 1999
Reelin (ECM protein)	*RELN*	Neurite outgrowth and neuronal synaptogenesis defects	LCH with pachygyria, marked cerebellar hypoplasia, and foliation defect	Borrell et al 1999a,b Hong et al 2000
L1 (ECM adhesion protein)	*L1CAM*		CRASH syndrome with callosal defect, retardation, adducted thumbs, spasticity, and hydrocephaly	Sztriha et al 2000

[a]Suspected role appears in parentheses.

[b]Primary evidence in *Drosophila* with relevance to mammalian systems demonstrated.

produce defects in neurite extension as well as axon pathfinding (compare Tables 1 and 2, Figure 2). For example, *reelin* mutation produces not only neuronal migration defects, but also abnormalities in neurite outgrowth (Borrell et al 1999a,b). In *Drosophila*, the cAbl tyrosine kinase produces defects of axonal fasciculation, and in mammals the kinase is capable of phosphorylating cdk5 (Zukerberg et al 2000). In turn, cdk5 and its activating subunit, p35, have both been localized to growth cones in the mouse, and mutations can interfere with neurite outgrowth, whereas p35 nulls reveal defects in callosal axon guidance (Kwon et al 1999, Nikolic et al 1998, 1996).

In addition to the tantalizing association of cAbl function with the mDab1 protein in the migration defects revealed by *scrambler* and *yotari* mice, another cAbl modulator, enabled, has been implicated in axonogenesis. For example, mice deficient in the Mena (mammalian enabled) protein display defects in neural tube closure and axonal commissure formation (Lanier et al 1999). Mena has been shown to bind directly to profilin, an actin binding protein that modulates actin polymerization (Lanier et al 1999, Suetsugu et al 1999). In *Drosophila*, both cAbl and profilin are required for axon extension (Wills et al 1999). In mammals the abl related gene (*Arg*) is a tyrosine kinase that is enriched in brain and colocalizes with cAbl and actin microfilaments (Koleske et al 1998). That double *Abl/Arg* nulls display embryonic lethality with severe neurulation defects indicates that the two kinases may compensate for loss of one another in neuronal migration defects.

Recently, a crucial ligand-receptor system for axonal pathfinding and midline decussation (crossing) has been identified in *Drosophila*, for which homologous elements are being found in mammals. The ligand, Slit, is an extracellular matrix protein required for midline glial and axon commissural pathfinding (Rothberg et al 1990). There are several Slit proteins that bind a family of receptors, Robo (roundabout), that control the axonal "decision" to cross midline structures (Bashaw et al 2000, Brose et al 1999, Kidd et al 1999). In flies the Robo receptor proteins appear to function upstream of opposing actions of cAbl and enabled (Bashaw et al 2000). In mammals Slits 1 and 2 and Robo 1 and 2 are expressed in forebrain, and human Slit-2 can collapse growth cones and repel hippocampal and olfactory axons, as well as modulate retinal axon pathfinding (Nguyen Ba-Charvet et al 1999, Ringstedt et al 2000).

Because the proposed actions of many genes involved in neurite extension entail remodeling of the actin cytoskeleton, it is likely that at least some of these influence neuronal migration as well. This will undoubtedly include actions of leading process extension and contractility elements that generate the net movement forward (Figure 1). Regulation of microtubule dynamics will clearly participate in both neurite extension and cell migration, though the impact on neurites of genes like *LIS1* and *DCX* has yet to be examined in any detail. A crucial aspect of future investigations will be characterization of the interface between regulation of the actin-based and microtubule-based cytoskeleton in response to signals presented to the cell.

SYNDROMES OF CORTICAL DISORGANIZATION

Although not necessarily a primary affector of neuronal migration, a number of important processes may result in heterotopic placement of neurons if disturbed. These syndromes warrant brief discussion, as they may ultimately bear on the fine-tuning of neuronal migration and certainly pertain to the establishment of cortical structure. A partial list appears in Table 3, where they are mentioned because either clinical observation or animal models have revealed neuronal heterotopia and cortical dysplasia phenotypes.

Dysplasia Associated with Altered Neurogenesis and Cell Survival

Cortical dysplasia may arise from disturbances in the primary genesis of neural elements, both in cell number and fate. A few candidate genes that could disrupt

TABLE 3 Summary of genes affecting neurogenesis and brain organization

		Mutation phenotype		
Proliferation/Apoptosis[a]	**Gene**	**Murine**	**Human**	**Reference**
TISH (unknown, recessive gene in seizure-prone rat)	*Tish*	DC/SBH-like rat mutant due to ectopic neural cell proliferation		Lee et al 1997 Lee et al 1998
EMX2 (transcription factor homologue of *Drosophila* segmentation gene empty spiracles)	*EMX2*	−/−: disorganized cortex with abnormal subplate and marginal zone development affecting radial glia	A rare cause of open lipped schizencephaly	Granata et al 1997 Mallamaci et al 2000
Rb (oncogene regulating G1 progression)	*pRB*	−/−: ectopic mitoses and apoptosis in brain		Lee et al 1992
Caspase-3 (enzyme required for apoptosis)	*CPP32*	−/−: shows increased cell numbers, displaced neurons		Kuida et al 1996
Cyclin D2 [G1 active subunit regulating cyclin-dependent kinase 4 (cdk4)]	*Ccnd2*	−/−: thinned cortex, small cerebellum, reduced neural proliferation, and increased apoptosis		Huard et al 1999
Cyclin D1 (G1-active subunit regulating cdk4)	*Ccnd1*	−/−: runted animal, thinned cortex, motor abnormalities suggesting spasticity		Sicinski et al 1995

[a]Suspected role appears in parentheses.

cortical histogenesis in this way have been examined with regard to their effects on brain organization. Other clinically recognized cortical malformations have been associated with mutation in genes recognized for their influence on neural fate determination.

Ectopic Neurogenesis At least two animal models have demonstrated that neural precursor proliferation can produce striking disruptions in brain histogenesis. The spontaneous appearance of an autosomal recessively transmitted mutation in the *tish* rat displays a phenotype that bears similarity to human DC/SBH (Lee et al 1997). *Tish* brain reveals a band of heterotopic neurons just beneath a relatively normal-appearing cortical gray matter, in fronto-parietal cortex. The *tish* phenotype suggests altered migration of a subpopulation of neurons toward the cortex. Surprisingly, however, pulse labeling with BrdU demonstrated that *tish* heterotopia arise from ectopic cell proliferation rather than impaired migration of young neurons just out of the cell cycle (Lee et al 1998). Band heterotopia in humans and *tish* represents an important example of similar phenotypes that arise from different mechanisms, and underscores the caveat that initial classification of a clinical syndrome as a neuronal migration or other defect must be tentative pending functional investigation once the causative gene is identified.

A second example of ectopic neurogenesis is found in mouse models that inactivate the retinoblastoma protein, Rb (Lee et al 1992). This nuclear phosphoprotein regulates passage of neural precursor cells through the G1 phase of the cell cycle. Complete inactivation of pRb is lethal by embryonic day 16, and brain is profoundly affected by multiple foci of ectopic mitoses as well as massive cell death (Lee et al 1992). Together, the *tish* and $pRb^{-/-}$ models indicate that ectopic cell proliferation is an important consideration when designing investigations of gene function associated with cortical malformation.

Altered Cell Survival Several genes involved in programmed cell death have been demonstrated in mouse models to result in neuronal displacements. A dramatic example is found in the *caspase-3* (*CPP32*) null mice (Kuida et al 1996). These animals are reduced in overall size, and brain is markedly abnormal, with areas of hyperplasia, reduced apoptosis, and heterotopia. Caspace-3 is a member of the ICE-protease family of enzymes that are required for the DNA fragmentation and chromatin condensation characteristic of apoptosis.

Microcephaly Defined as head size less than -2 standard deviations below normative curves for age, microcephaly comprises a very heterogeneous group of disorders. This is true even when considering only congenital microcephaly, defined as head circumference less than -2 standard deviations from the mean at birth. Recent reports of magnetic resonance imaging in congenital microcephaly have recognized multiple phenotypic patterns of small brains, including those with the following: normal gyral pattern, simplified gyral pattern, agenesis of the corpus callosum, thickened cortical gray matter (a.k.a. microlissencephaly), and other

cortical dysplasia including polymicrogyria (Barchovich et al 1998, Sztriha et al 1998, 1999, Peiffer et al 1999). Among affected patients, the severity of cognitive and motor impairment and epilepsy correlate with both head size and the pattern of cortical malformation. Inherited genetic causes of microcephaly are indicated by the occurrence in siblings reported for many of these subtypes (Sztriha et al 1998, 1999; Peiffer et al 1999). The observation of dysplastic forms with thickened cortical gray matter (microlissencephaly) and neuronal heterotopia suggests that neuronal migration abnormalities contribute to the pathogenesis of some microcephalic children (Barkovich et al 1998).

At least 5 loci for congenital microcephaly have been mapped, including 8p22, 19q13, 9q34, 1q31, and 15q (Jackson et al 1998, Jamieson et al 1999, Roberts et al 1999, Moynihan et al 2000, Pattison et al 2000). Candidate genes for microcephaly include those that decrease proliferation in the germinal neuroepithelium or that increase apoptotic cell loss. Examples of cell cycle regulatory genes that are candidates are found in the cyclins D1 and D2. These are activating noncatalytic subunits of cyclin-dependent kinases, principally cdk4, that regulate the mid-G1 phase transition (Xiong et al 1992). Passage of cells through this restriction point commits the cell to a round of division. Null mice lacking the cyclin D1 have small brains, are small in stature and manifest motor abnormalities, suggesting central nervous system developmental defects (Sicinski et al 1995). Interestingly, although cell cycle regulatory genes would be expected to produce small but otherwise normal appearing brains, animal models suggest these genes may also affect brain organization. For example, cyclin D2 nulls are of normal body size but display reduced cerebellar and cerebral cortical volumes with altered cytoarchitecture owing to a combination of decreased cell proliferation and increased apoptosis (Huard et al 1999).

Malformations Not Yet Classified

These represent disorders in which neurons are observed to be out of place, but lack of gene identification or adequate genetic models prevents definitive classification of the primary defect.

Polymicrogyria (PMG) In this disorder, neurons move out to the cortical surface but organize abnormally to produce multiple small gyri. Radiographically, PMG is characterized by multiple small gyri with shallow sulci and white-matter interdigitation giving the cortex a roughened appearance (Barkovich et al 1999). Thick magnetic resonance sections can give the appearance of pachygyria because signal intensities are averaged and microgyri are missed, so that images constructed at <4 mm intervals may be necessary to detect PMG. The surface of the brain may be variably smooth, when the outer molecular layer fuses over the microsulci, or may be irregular.

Pathologically, two patterns of PMG are recognized: (*a*) "four-layered" PMG, in which cortex comprises a molecular layer, an organized outer layer, a cell sparse layer, and a disorganized inner layer and (*b*) a completely disorganized "unlayered"

microgyrus. PMG can arise from several intrauterine insults including hypoxemia with cortical laminar necrosis. This hypothesis of intrauterine insult is in part derived from experimental models in the rat produced by cortical lesions such as focal freezing injury (Jacobs et al 1999). However, the detection of PMG in several affected family members indicates inherited causes as well. Lesion experiments suggest mechanisms that interfere with radial glial function and secondary disturbances of neuronal migration, though this is far from established as a general rule. That involvement of radial glia may not always be required is suggested by interesting in vitro experiments that produce heterotopia beneath the marginal zone of cortical slices exposed to the trophic factor NT4 (Brunstrom et al 1997). This malformation appears to arise from aberrant migration of interneurons from the ganglionic eminence (Brunstrom & Pearlman 2000, Eisenstat et al 1999, Anderson et al 1999).

Focal patterns of PMG and transmission within families suggest several causative genes (Barkovich et al 1999). Diffuse PMG involves widespread areas of cortex and is most likely to have epigenetic causes, such as intrauterine infection or toxic exposure producing encephalopathy, though some causes may be genetic. Thirteen patients with PMG confined to frontal cortex have recently been reported. All 13 were sporadic, though there was parental consanguinity in 2 of the families, raising the possibility of autosomal recessive inheritance (Sztriha & Nork 2000, Guerrini et al 2000). Studies in 12 kindreds with perisylvian PMG indicate genetic hetrogeneity with both X-linked and autosomal (dominant with incomplete penetrance or recessive) patterns (Guerreiro et al 2000, Borgatti et al 1999). PMG involving parieto-occipital cortex has been reported in nine individuals; however, an inheritance pattern has not been established (Guerrini et al 1997).

Schizencephaly The hallmark of schizencephaly ("split brain") is a cleft in the cerebral cortex, which may be unilateral or bilateral, that extends through the cortex to the lateral ventricular surface. This may appear as a wide cleft (open lipped) or a narrow groove (closed lipped) that is typically lined by gray matter polymicrogyria. The transcription factor, *EMX2*, accounts for a minority (likely rare cases) of open-lipped schizencephaly (Faiella et al 1997, Granata et al 1997). *EMX2* is a mammalian homologue of the *Drosophila* homeotic gene *empty spiracles*, involved in cell fate determination (Simeone et al 1992). It is expressed in the cortical ventricular zone of mammals. Mice lacking *EMX2* expression initially produce reelin at the time of cortical preplate formation but later lose this protein with adverse consequences for radial glial development, neuronal migration, and cortical plate formation (Mallamaci et al 2000a). In addition, lack of *EMX2* produces shifts in cerebral cortical–area development, such that anterior-lateral cortical areas predominate over medial-caudal identities (Bishop et al 2000, Mallamaci et al 2000b). This may in part account for the regional localization of the most severely affected cortex in Scizencephaly. *EMX2* demonstrates that gene action determining the fate of cells can have secondary effects on migration away from the germinal neuroepithelium and subsequent cortical organization.

SUMMARY

The number and nature of gene mutations that can disrupt neuronal migration is large and growing. This is not surprising, given the impressive array of molecular steps that must be taken to move a cell and position it within a system as complex as the brain. Through investigations stimulated by human clinical syndromes and animal models of brain malformation, the pieces of this intricate puzzle are coming into view and are beginning to fall into a fascinating pattern. Clearly, these genes are subserving multiple functions, and their actions will be found to span artificial boundaries between primary neurogenesis, cell survival, migration, neurite extension, axon pathfinding, and synaptogenesis. This fundamental knowledge will assist formulation of strategies to promote repair and regeneration of brain damaged by trauma, stroke, maldevelopment, mechanisms of immunity, or aging.

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