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Periventricular Heterotopia and the Genetics of Neuronal Migration in the Cerebral Cortex

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In recent years, remarkable contributions to our understanding of how the brain develops have come from the field of genetics. The study of brain development is important, not only to further our understanding of this complex phenomenon, but because gross brain malformations are now recognized to cause significant proportions of cognitive and neurologic disorders. When the cerebral cortex fails to form properly, the result is often severe mental retardation. Even mild dysgenesis of the cortex is frequently associated with epilepsy. Modern genetics affords us the opportunity to explain these developmental mishaps at a molecular level and provides critical insight into nature's program for brain development, adding an important new dimension to the extensive neuroanatomic work of the last 100 years.

Neurons that populate the adult cortex are not born in place. Instead, they are born deep within the brain, in the germinal layer of the ventricular zone, which develops from the lining of the lumen of the neural tube. To get to their proper adult location, most cerebral cortical neurons migrate hundreds to thousands of cell body lengths along tracks of radially oriented glial cells, which stretch from the ventricular zone to the outer, pial surface. These cortical neurons migrate in waves to build layers in the cortex, with each successive wave migrating past earlier-born neurons to add a more superficial layer (fig. 1*A*). This migration pattern is referred to as "inside out" and must be faithfully executed for the adult cortex to form and function properly. When migration is complete, the cortex is a six-layered structure (fig. 1*B*), with each layer comprising different types of neurons that form discrete connections within the CNS and perform distinct functions.

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Several groups of researchers, hoping to identify the causes of various epilepsies and cognitive disorders, have applied genetics to the study of cerebral cortex development and neuronal migration. These cloning efforts have been remarkably successful over the past few years, uncovering several genes that, when mutated, cause disorders of neuronal migration and cerebral cortical development in mice and in humans.

Insights from Mouse Mutants

In the classic mouse mutant, reeler, the layers of the cortex are nearly inverted relative to the wild type, and the cerebellum is significantly underdeveloped. The reeler gene, *Reln,* was cloned in 1995 (D'Arcangelo et al.), and the protein, reelin, was found to resemble tenascin and other large extracellular matrix molecules. On the basis of its restricted pattern of expression in the brain (fig. 1*A*), reelin is thought to act as a stop signal for migrating cortical neurons (D'Arcangelo et al. 1995) as well as cerebellar Purkinje cells (Miyata et al. 1996), instructing them to release from the radial glial cells and to begin to differentiate. The receptor for reelin has not yet been identified, however, and thus the mechanism by which this protein transmits a signal to migrating neurons is still unknown.

The scrambler mouse is behaviorally and morphologically indistinguishable from the reeler mouse (Gonzalez et al. 1997), an observation that led many to expect the scrambler gene to encode the receptor for the reelin protein. The identification of the scrambler gene as *Dab1* (Sheldon et al. 1997; Ware et al. 1997), encoding a cellular protein that interacts with nonreceptor tyrosine kinases like Src and Abl (Howell et al. 1997), came as a surprise. However, recent evidence suggests that Dab1 and reelin do lie within a common signaling pathway. Dab1 is upregulated in the absence of reelin in vivo (Rice et al. 1998), and reelin induces phosphorylation of Dab1 when applied to neurons in culture (Howell et al. 1999). It is therefore possible that Dab1 binds an intracellular domain of the receptor for reelin, and it may be possible

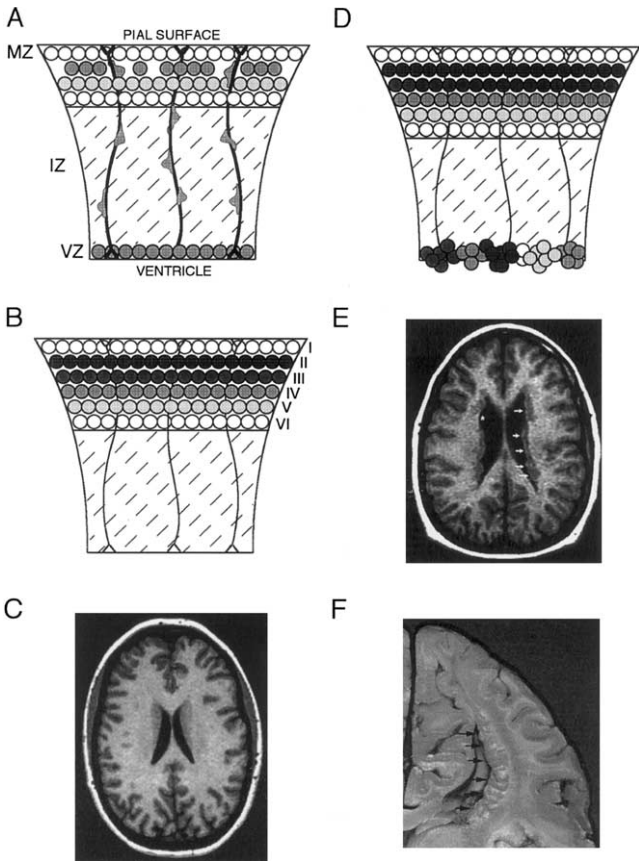

Figure 1 Normal and PH cerebral cortical development. *A,* Neurons are formed deep within the germinal layer of the ventricular zone (VZ) and migrate through the cell sparse intermediate zone (IZ). Newly formed neurons migrate along radially oriented glial cells, past all earlier-formed neurons, to form a new superficial layer in the cortex. The exception to this rule is the marginal zone (MZ), which remains the external layer throughout development though its neurons are the earliest formed. These MZ, or layer I, cells secrete reelin and may act as a stop signal for subsequent waves of migrating neurons. Earlier-formed neurons are lighter; later-formed neurons are shaded darker. *B,* The mature cortex has six layers, each with different cell types that make distinct connections within the CNS. After migration is complete, the radial glial cells lose their extended morphologic structure and condense into astrocytes (not shown). *C,* A magnetic resonance image (MRI) of a normal human cortex, showing ventricles with a smooth neuroepithelial lining. *D,* In PH, subsets of neurons of various types fail to exit the VZ and remain as clumps, or nodules, of differentiated neurons, often making connections within the CNS. A proper, six-layered cortex also forms. *E,* MRI of a PH cortex. Arrows indicate a continuum of nodules lining the neuroepithelium of the right ventricle. The ventricles also appear enlarged. An asterisk indicates an area of the left ventricle that is free from heterotopias. *F,* A postmortem section of a PH cortex, with arrows again indicating a continuous lining of nodules along the right ventricle.

to isolate this elusive reelin receptor by taking advantage of this interaction.

The targeted disruption of C*dk5,* which encodes a protein that resembles cyclin-dependent kinases (Gilmore et al. 1998), leads to defects in cortical lamination that are similar but not identical to the defects seen in the reeler and scrambler mice. Similar defects occur in mice that lack p35, a brain-specific regulator of Cdk5 (Chae et al. 1997). Like the reeler and scrambler mice, the C*dk5*-deficient mice have a severe defect of the cerebellum, likely reflecting the importance of granule cell migration in the development of this structure and indicating that neuronal migration in both the cortex and cerebellum may employ a common mechanism. Recent work suggests that Cdk5 and p35 act in a signal transduction pathway with the small GTPase Rac and the p21-activated protein kinase family member Pak1 (Nikolic et al. 1998). Rac and Pak1 are known to localize to the leading edge of neurites during outgrowth through interactions with the actin cytoskeleton (Nikolic et al. 1998), and it may be through this cytoskeletal interaction that Cdk5/p35 regulates neuronal migration.

Human Disorders of Neuronal Migration

Two genes have been identified recently that, when mutated in humans, produce a severe cortical defect called lissencephaly, or "smooth brain." In lissencephaly, neurons migrate only partially toward their proper cortical destination so that a mature cortex, possessing gyri and sulci, fails to form. Patients are left with profound mental retardation and epilepsy. *LIS1,* the gene for an autosomal form of lissencephaly, was isolated in 1993 (Reiner et al.) and encodes a protein similar to the β subunit of heterotrimeric G proteins. LIS1 functions as a regulatory subunit of platelet-activating factor acetylhydrolase (PAF-AH), an enzyme that degrades the bioactive lipid PAF (Hattori et al. 1994). A reduction in the migration of cerebellar granule cells in vitro occurred on treatment with a PAF agonist (Bix and Clark 1998), implying that LIS1 function in PAF-AH is related to its essential role in migration. Interestingly, LIS1 has been shown to colocalize with microtubules and to promote their stabilization (Sapir et al. 1997), and an ortholog of LIS1 in *Aspergillus nidulans,* nudF, mediates nuclear translocation, probably by interacting with microtubules (Morris et al. 1998). Thus, it may be through microtubules that LIS1 exerts it effects on migration, perhaps as a component of PAF-AH.

The second lissencephaly syndrome, whose gene was recently cloned, is X-linked. Female patients present as mosaics with a less severe, although striking, "double cortex" phenotype, in which a second band of cortical neurons exists within the white matter below the true cortex. The gene for this double-cortex/X-linked lissencephaly syndrome, doublecortin (*DCX*), encodes a novel protein (des Portes et al. 1998; Gleeson et al. 1998). Extensive mutational analysis (Gleeson et al. 1999) and sophisticated protein modeling have uncovered potential

protein-protein interaction domains of DCX, and recent work has again implicated an interaction with microtubules through which DCX may exert its effect on migration (Gleeson et al., in press). The interaction of both LIS1 and DCX with microtubules may explain the striking similarities between the lissencephalic phenotypes produced by mutations in these two genes. A direct molecular link between these proteins has yet to be demonstrated, however.

Although it is apparent that more than one molecular mechanism will be defined by the various murine and human neuronal migration disorders mentioned, these disorders do share one common feature. In each disorder, cortical neurons migrate some distance, sometimes completely, into the developing cortex. A human disorder that seems to violate this central tenet, and that therefore might define an additional molecular mechanism that is absolutely required for neuronal migration of any kind, is periventricular heterotopia (PH).

PH

PH differs from each of the mentioned disorders of neuronal migration in that migration is neither misdirected nor interrupted; instead, there is a total failure of migration of some neurons. Consequently, many neurons remain in the ventricular zone as clumps or nodules of differentiated neurons, while the remainder of the neurons migrate normally and completely to form the proper, six-layered cortex (fig. 1*D–F*). This cortex functions surprisingly well, despite the presence of a large population of ectopic neurons, as most patients with PH have normal intelligence. PH is an X-linked dominant disorder that displays embryonic hemizygous male lethality (Eksioglu et al. 1996). PH is therefore generally regarded as a cell-autonomous mosaic phenotype, in females, due to random X inactivation, where neurons that express the mutant X chromosome fail to migrate and neurons that express the normal X chromosome migrate properly. The major neurologic manifestation in female patients is epilepsy, ranging in severity from mild to intractable, with the age at onset usually in the mid teens. Many patients with PH also present with cerebellar anomalies, a common finding among disorders of neuronal migration, and some show defects of the corpus callosum (Fox et al. 1998). This latter finding may suggest some additional defect in long-range axonal path finding in these patients.

The identification of the PH gene began with linkage mapping to Xq28 (Eksioglu et al. 1996), which was followed by the study of a chromosomal rearrangement and candidate gene analysis. This work implicated the well-characterized filamin 1 (*FLN1*) gene (also known as FLNA, actin-binding protein 280, ABP-280, and nonmuscle filamin) as causative in PH (Fox et al. 1998). We identified several loss-of-function, likely null, mutations at the 5′ end of the coding region in a large pedigree, a small pedigree, and several sporadic patients, and we demonstrated for the first time that FLN1 shows a high level of expression in the developing mammalian brain (Fox et al. 1998).

FLN1

FLN1 is a 280-kD actin-binding protein composed almost entirely of 24, 96 amino acid repeats, interrupted only by two flexible hinge regions (Gorlin et al. 1990). The exception is the N terminus, which encodes an actin-binding domain similar to that of dystrophin. The 24th repeat is truncated, allowing dimerization of two FLN1 molecules at the C terminus (Gorlin et al. 1990). FLN1 dimers bind membrane-associated proteins such as β1 and β2 integrins (Sharma et al. 1995; Loo et al. 1998), tissue factor (Ott et al. 1998), and presenilin 1 (Zhang et al. 1998). FLN1 can also bind other membrane-associated molecules, such as glycoprotein Ibα, through repeats further from the C terminus (Meyer et al. 1997).

FLN1 is the most widely expressed of the family of filamins, appearing to some degree in most cell types except muscle. The filamins were originally identified as high–molecular weight biochemical activities that caused purified actin to gel and precipitate (Hartwig and Stossel 1975). FLN1 promotes orthogonal branching of actin filaments (Gorlin et al. 1990) and is important for coagulation and vascular development. FLN1 binds the intracellular domain of glycoprotein Ibα in platelets (Meyer et al. 1997). Mutation of glycoprotein Ibα results in the bleeding disorder known as Bernard-Soulier syndrome (Nurden et al. 1981). FLN1 also binds the intracellular domain of tissue factor in vascular cells. The extracellular domain of tissue factor initiates the extrinsic coagulation cascade, and tissue factor also functions to maintain vascular integrity in the developing embryo (Ott et al. 1998). Targeted disruption of tissue factor in mice causes embryonic lethality due to widespread hemorrhage (Bugge et al. 1996). These coagulation and vascular-related functions of FLN1 likely account for the prenatal male lethality observed in most pedigrees, a hypothesis supported by the birth of a male infant to a mother with PH, who shared her affected haplotype, and who died postnatally of severe, widespread hemorrhage (Fox et al. 1998).

FLN1 is important for the migration of several nonneural cell types, such as macrophages (Stendahl et al. 1980) and cultured melanocytes (Cunningham et al. 1992). Melanocytes lacking FLN1 show defects in filopodia formation and abnormal surface blebbing, which are corrected on transfection with FLN1-expressing clones (Cunningham et al. 1992). Further, melanocytes lacking FLN1 fail to accumulate actin at sites of me-

chanical stress (Glogauer et al. 1998), implying a necessary role for FLN1 in promoting the assembly of the cortical actin network. Motile *Dictyostelium* amoebae that lack ABP-120, a FLN1 homologue, show profound defects in actin cross-linking and cytoskeletal structure (Saxe 1999 [in this issue]) that disrupts pseudopod formation, cell motility, and chemotaxis (Cox et al. 1996). Restoring ABP-120 activity rescues each of these phenotypes. Taken together, these findings argue strongly that FLN1 creates or maintains actin networks at the leading edge of motile cells that are required for the migration of these cells.

FLN1 in the Developing Cortex

FLN1 may act in migrating neurons of the cortex the same way it acts in nonneural, migratory cell types, by structuring actin networks at the leading edge of motile cells. It is not surprising that the actin cytoskeleton is essential for migration of axonal growth cones and neurons because structured actin networks are required for filopodia and lamellipodia formation within the leading edge of migrating neurons (Rivas and Hatten 1995) and migrating growth cones (Letourneau and Shattuck 1989). Treatment of migrating cerebellar granule cells with cytochalasin C to disrupt actin filaments completely blocks migration (Rivas and Hatten 1995). Cross-linking of actin filaments in lamellipodia and bundling of actin filaments in filopodia are important for the formation of these structures and therefore for leading edge migration in both growth cones and migrating neurons. FLN1 could be required for promoting or maintaining these actin networks, and it may act in conjunction with the Cdk5/p35/Rac/Pak1 complex to regulate neurite outgrowth (Nikolic et al. 1998). An adapter molecule, Trio, that binds to and activates Rac, also binds FLN1 (Bellanger et al. 1998). Thus, the association of Cdk5/p35 with the cytoskeleton might be mediated through FLN1, or FLN1 may be a substrate for Cdk5 phosphorylation. This latter idea is supported by the identification of several potential Cdk5 phosphorylation sites near the C terminus of FLN1 (Fox et al. 1998).

This first model of FLN1 function is straightforward, postulating that, in FLN1-deficient neurons, part of the essential migratory motor is defective and that these defective neurons are wholly incapable of migration. An alternative model proposes that FLN1 acts earlier in development, not as a component of the migratory motor but instead as a component of a switch that is required for a neuron to become competent for subsequent migration. In the latter model, FLN1 still functions by structuring actin networks at the cell periphery, but instead of acting at the leading edge of the migrating neuron, FLN1 maintains a static focal contact between a stationary neuron and a neighboring radial glial cell. This tight association may facilitate the exchange of chemical signals between the neuron and glial cell that promote neuronal migration. Candidates for mediating this association may be found in the family of integrins, which FLN1 is known to bind (Sharma et al. 1995; Glogauer et al. 1998; Loo et al. 1998) and which are required for neuron-glial interactions in the developing cerebellum and cortex (Anton et al. 1999).

Other models may be invoked to explain the total failure of neuronal migration in PH. Unfortunately, it will not be practical to distinguish among the possible roles for FLN1 in the brain by studying the human cortex. Generation of a targeted disruption of the *Fln1* gene in the mouse may reproduce the PH phenotype in an organism more amenable to anatomic and molecular genetic studies.

Conclusions

We are in the earliest stages of understanding the genetics of development of the cerebral cortex. Although no clear molecular pathway has yet been revealed, genetic analyses appear to have defined at least three distinct stages of migration. The first is a premigratory stage, during which FLN1 bestows migrational competence to newborn neurons. The second stage is the migratory phase, which depends upon the function of DCX and LIS1, possibly for nuclear migration, and which may also rely upon the Cdk5/p35/Rac/Pak1 complex to regulate actin dynamics at the leading edge of migrating neurons. In the third and final stage, reelin and Dab1 transmit a stop signal to neurons, instructing them to end migration and to release from radial glia. The concerted effort of the players at each stage guides a neuron from just after its birth in the ventricular zone, through its long migration into and through the developing cortex and until it comes to rest in a new cortical layer.

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References

Anton ES, Kreidberg JA, Rakic P (1999) Distinct functions of α3 and α(v) integrin receptors in neuronal migration and

laminar organization of the cerebral cortex. Neuron 22: 277–289

Bellanger JM, Zugasti O, Lazaro JB, Diriong S, Lamb N, Sardet C, Debant A (1998) Role of the multifunctional Trio protein in the control of the Rac1 and RhoA gtpase signaling pathways. C R Seances Soc Biol Fil 192:367–374

Bix GJ, Clark GD (1998) Platelet-activating factor receptor stimulation disrupts neuronal migration in vitro. J Neurosci 18:307–318

Bugge TH, Xiao Q, Kombrinck KW, Flick MJ, Holmback K, Danton MJ, Colbert MC, et al (1996) Fatal embryonic bleeding events in mice lacking tissue factor, the cell-associated initiator of blood coagulation. Proc Natl Acad Sci USA 93:6258–6263

Chae T, Kwon YT, Bronson R, Dikkes P, Li E, Tsai LH (1997) Mice lacking p35, a neuronal specific activator of Cdk5, display cortical lamination defects, seizures, and adult lethality. Neuron 18:29–42

Cox D, Wessels D, Soll DR, Hartwig J, Condeelis J (1996) Re-expression of ABP-120 rescues cytoskeletal, motility, and phagocytosis defects of ABP-120-Dictyostelium mutants. Mol Biol Cell 7:803–823

Cunningham CC, Gorlin JB, Kwiatkowski DJ, Hartwig JH, Janmey PA, Byers HR, Stossel TP (1992) Actin-binding protein requirement for cortical stability and efficient locomotion. Science 255:325–327

D'Arcangelo G, Miao GG, Chen SC, Soares HD, Morgan JI, Curran T (1995) A protein related to extracellular matrix proteins deleted in the mouse mutant reeler. Nature 374: 719–723

des Portes V, Pinard JM, Billuart P, Vinet MC, Koulakoff A, Carrie A, Gelot A, et al (1998) A novel CNS gene required for neuronal migration and involved in X-linked subcortical laminar heterotopia and lissencephaly syndrome. Cell 92: 51–61

Eksioglu YZ, Scheffer IE, Cardenas P, Knoll J, DiMario F, Ramsby G, Berg M, et al (1996) Periventricular heterotopia: an X-linked dominant epilepsy locus causing aberrant cerebral cortical development. Neuron 16:77–87

Fox JW, Lamperti ED, Eksioglu YZ, Hong SE, Feng Y, Graham DA, Scheffer IE, et al (1998) Mutations in filamin 1 prevent migration of cerebral cortical neurons in human periventricular heterotopia. Neuron 21:1315–1325

Gilmore EC, Oshima T, Goffinet AM, Kulkarni AB, Herrup K (1998) Cyclin-dependent kinase 5-deficient mice demonstrate novel developmental arrest in cerebral cortex. J Neurosci 18:6370–6377

Gleeson JG, Allen KM, Fox JW, Lamperti ED, Berkovic S, Scheffer I, Cooper EC, et al (1998) Doublecortin, a brain-specific gene mutated in human X-linked lissencephaly and double cortex syndrome, encodes a putative signaling protein. Cell 92:63–72

Gleeson JG, Lin PT, Flanagan LA, Walsh CA. Doublecortin is a microtubule associated protein and is expressed widely by migrating neurons. Neuron (in press)

Gleeson JG, Minnerath SR, Fox JW, Allen KM, Luo RF, Hong SE, Berg MJ, et al (1999) Characterization of mutations in the gene doublecortin in patients with double cortex syndrome. Ann Neurol 45:146–153

Glogauer M, Arora P, Chou D, Janmey PA, Downey GP, McCulloch CA (1998) The role of actin-binding protein 280 in integrin-dependent mechanoprotection. J Biol Chem 273: 1689–1698

Gonzalez JL, Russo CJ, Goldowitz D, Sweet HO, Davisson MT, Walsh CA (1997) Birthdate and cell marker analysis of scrambler: a novel mutation affecting cortical development with a reeler-like phenotype. J Neurosci 17:9204–9211

Gorlin JB, Yamin R, Egan S, Stewart M, Stossel TP, Kwiatkowski DJ, Hartwig JH (1990) Human endothelial actin-binding protein (ABP-280, nonmuscle filamin): a molecular leaf spring. J Cell Biol 111:1089–1105

Hartwig JH, Stossel TP (1975) Isolation and properties of actin, myosin, and a new actin-binding protein in rabbit alveolar macrophages. J Biol Chem 250:5696–5705

Hattori M, Adachi H, Tsujimoto M, Arai H, Inoue K (1994) Miller-Dieker lissencephaly gene encodes a subunit of brain platelet- activating factor acetylhydrolase. Nature 370: 216–218

Howell BW, Gertler FB, Cooper JA (1997) Mouse disabled (mDab1): a Src binding protein implicated in neuronal development. EMBO J 16:121–132

Howell BW, Herrick TM, Cooper JA (1999) Reelin-induced tryosine phosphorylation of disabled-1 during neuronal positioning. Genes Dev 13:643–648

Letourneau PC, Shattuck TA (1989) Distribution and possible interactions of actin-associated proteins and cell adhesion molecules of nerve growth cones. Development 105: 505–519

Loo DT, Kanner SB, Aruffo A (1998) Filamin binds to the cytoplasmic domain of the β1-integrin: identification of amino acids responsible for this interaction. J Biol Chem 273:23304–23312

Meyer SC, Zuerbig S, Cunningham CC, Hartwig JH, Bissell T, Gardner K, Fox JE (1997) Identification of the region in actin-binding protein that binds to the cytoplasmic domain of glycoprotein IBα. J Biol Chem 272:2914–2919

Miyata T, Nakajima K, Aruga J, Takahashi S, Ikenaka K, Mikoshiba K, Ogawa M (1996) Distribution of a reeler gene-related antigen in the developing cerebellum: an immunohistochemical study with an allogeneic antibody CR-50 on normal and reeler mice. J Comp Neurol 372:215–228

Morris NR, Efimov VP, Xiang X (1998) Nuclear migration, nucleokinesis and lissencephaly. Trends Cell Biol 8:467–470

Nikolic M, Chou MM, Lu W, Mayer BJ, Tsai LH (1998) The p35/Cdk5 kinase is a neuron-specific Rac effector that inhibits Pak1 activity. Nature 395:194–198

Nurden AT, Dupuis D, Kunicki TJ, Caen JP (1981) Analysis of the glycoprotein and protein composition of Bernard-Soulier platelets by single and two-dimensional sodium dodecyl sulfate–polyacrylamide gel electrophoresis. J Clin Invest 67:1431–1440

Ott I, Fischer EG, Miyagi Y, Mueller BM, Ruf W (1998) A role for tissue factor in cell adhesion and migration mediated by interaction with actin-binding protein 280. J Cell Biol 140:1241–1253

Reiner O, Carrozzo R, Shen Y, Wehnert M, Faustinella F, Dobyns WB, Caskey CT, et al (1993) Isolation of a Miller-Dieker lissencephaly gene containing G protein β-subunit-like repeats. Nature 364:717–721

Rice DS, Sheldon M, D'Arcangelo G, Nakajima K, Goldowitz

D, Curran T (1998) Disabled-1 acts downstream of Reelin in a signaling pathway that controls laminar organization in the mammalian brain. Development 125:3719–3729

Rivas RJ, Hatten ME (1995) Motility and cytoskeletal organization of migrating cerebellar granule neurons. J Neurosci 15:981–989

Sapir T, Elbaum M, Reiner O (1997) Reduction of microtubule catastrophe events by LIS1, platelet-activating factor acetylhydrolase subunit. EMBO J 16:6977–6984

Saxe CL (1999) Learning from the slime mold: *Dictyostilium* and human disease. Am J Hum Genet 65:25–30 (in this issue)

Sharma CP, Ezzell RM, Arnaout MA (1995) Direct interaction of filamin (ABP-280) with the β 2-integrin subunit CD18. J Immunol 154:3461–3470

Sheldon M, Rice DS, D'Arcangelo G, Yoneshima H, Nakajima K, Mikoshiba K, Howell BW, et al (1997) Scrambler and yotari disrupt the disabled gene and produce a reeler-like phenotype in mice. Nature 389:730–733

Stendahl OI, Hartwig JH, Brotschi EA, Stossel TP (1980) Distribution of actin-binding protein and myosin in macrophages during spreading and phagocytosis. J Cell Biol 84: 215–224

Ware ML, Fox JW, Gonzalez JL, Davis NM, Lambert de Rouvroit C, Russo CJ, Chua SC Jr, et al (1997) Aberrant splicing of a mouse disabled homolog, mdab1, in the scrambler mouse. Neuron 19:239–249

Zhang W, Han SW, McKeel DW, Goate A, Wu JY (1998) Interaction of presenilins with the filamin family of actin-binding proteins. J Neurosci 18:914–922