New Directions in Neuronal Migration

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Over the past decade, genetic analyses have yielded a more molecular view of neuronal migration and its role in central nervous system development. We now realize that many of the molecular mechanisms that guide migrations in invertebrates are recapitulated in the vertebrate nervous system. These mechanisms guide dorsoventral and anterior-posterior migrations and merge with radial migratory pathways that are prominent in the development of the mammalian cortex. This review discusses the choreography of these different migratory mechanisms within the context of genetic approaches that have defined their molecular mechanisms.

The migration of immature neurons from germinal zones to specific positions where axon-target interactions occur is a critical step in the development of the synaptic circuitry of the brain. During development of the worm *Caenorhabditis elegans*, very few cells move from the positions where they are generated. Only 12 cell populations migrate, including three classes of neurons (HSN, CAN, and Q neuroblasts), somatic gonad precursors, and sex myoblasts (*1*–*3*). The more complex body plan of the fruitfly *Drosophila* is reflected in more widespread cell migration (*3*). In vertebrates, many cells undergo remarkable cell migrations, including the cells of the gonads, kidney, and the immune and nervous systems. Neuronal migration culminates in the formation of layered cortical structures in mammals where a novel form of migration, across the radial plane of the neural tube, develops.

Studies on neuronal migration in *C. elegans* have identified numerous genes that encode chemoattractants or receptors important for neuroblast migration along the body axis, either along the dorsoventral (DV) axis or anterior-posterior (AP) axis (Fig. 1) (*1*–*3*). The most studied of these is *unc-6* (also called *unc-6/Netrin1*), which is required for DV but not AP migrations in *C. elegans*. *unc-6* encodes a protein secreted by ventral midline cells, which guides the migration of cells in the dorsal direction via the receptor UNC5 and ventrally via the receptor UNC40 (*4*). As discussed later, UNC-6/Netrin1 and its receptors are critical for early cell migrations along the DV axis of vertebrates as well. With regard to the AP axis of *C. elegans*, MIG13 is a transmembrane protein that acts nonautonomously in anterior migrations of Q neurons (*5*) The expression of MIG13 is regulated by Hox gene activity, such that increasing doses of MIG13 causes cells to migrate further anterior. In *C. elegans*, *vab-8* functions in posterior migrations (*6*). The *vab-8* locus encodes two isoforms of an intracellular protein, one of which contains a kinesin-like motor domain. The general schema seen in *C. elegans*, of migrations along the central axes of the embryo via global positioning system genes, is now appreciated in vertebrate embryos.

Dorsoventral Migrations in Vertebrates

The *unc-6/Netrin1* mechanism is involved in the developing cerebellar system. In the cerebellum, beginning on about embryonic day 12 in the mouse, proliferating progenitor cells located along the edges of the rhombic lip at the mes/metencephalon border begin to migrate over the surface of the ventricle and around the circumference of the neural tube. Precursors of cerebellar granule neurons move in a dorsorostral pathway to cover the surface of the emerging anlage between embryonic days 12 and 16 (Fig. 2). In the developing chick embryo, real-time imaging has revealed a temporal relation between the time of emergence of cells from the rhombic lip and their migration routes (*7*, *8*). Although a small population of cells from the rostral rhombic lip migrate ventrally, following the chemoattractant signal of UNC6/Netrin1, EGL cells of the cerebellum are repelled by netrin1 and move dorsorostrally across the surface of the anlagen. Indeed, progenitor cells overshoot the cerebellar territory in the spontaneous neurological mutant mouse *Unc5h3*, a disruption in a gene similar to *unc-5*. Thus, the cerebellar cortex forms, in part, as neurons evade the repulsive signal of the UNC6/Netrin1 guidance system.

Along the caudal portion of the rhombic lip, precursor cells of the precerebellar nuclei of the brainstem migrate from the rhombic lip toward the ventral midline, around the circumference of the neural tube, in a dorsal to ventral trajectory. These cell populations find netrin1 an attractive guidance cue and fail to migrate in mutant mice lacking DCC/UNC40 (*9*). Within the brainstem, the cells coalesce to form the inferior olive, a precerebellar nucleus that projects the climbing fiber afferents to the Purkinje cells. The basilar pons, another precerebellar nucleus in the brainstem, which projects mossy fiber afferents to the granule cells of the cerebellar cortex, also forms by DV migrations under the control of Netrin1 (*10*, *11*). These progenitors undergo a DV migration and use UNC6/Netrin1 as a chemoattractant in their migrations. Thus, the axonal guidance system Netrin1/UNC6 plays a critical role in the formation of the cerebellar system.

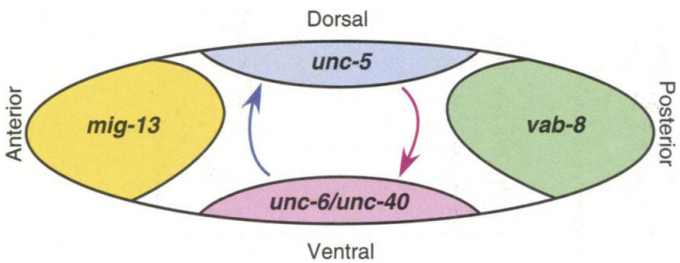

Fig. 1. Migratory pathways of neurons in *C. elegans* (*1*). UNC6/Netrin1 provides a guidance cue at the ventral midline (purple). Repulsion by UNC5 directs cells in a dorsal pathway (blue), whereas attraction by UNC6 or UNC40 directs cells ventrally. The membrane receptor MIG13 provides an anterior guidance system (yellow), whereas *vab-8* encodes two proteins for posterior cell migrations (green), one of which contains a kinesin domain.

Tangential Migrations in the Telencephalon

Another DV migration occurs in the forebrain, where proliferating precursor cells in the progenitor zone of the basal ganglia, the lateral and medial ganglionic eminences (LGE and MGE, respectively), migrate in a ventral to dorsal direction. This DV migration has been defined more precisely in genetic experiments using tissue from mice lacking the transcription factors *Dlx1,2* and *Nkx2.1* (*12*) With this tissue, it is possible to discern two populations of GABAergic inter-

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neurons migrating into the cortex. An early population of cells migrates dorsally from the MGE into the cortex, and a later population migrates along this trajectory from the LGE. The importance of this ventral to dorsal mode of migration is evidenced by the rather amazing fact that the GABAergic neurons comprise about 20% of the total neuronal population in the cortex. In addition to sending cells dorsally into the overlying cortex, the lateral ganglionic eminence also provides cells for the subventricular zone of the cortex. The migration of GABAergic neuroblasts from the MGE into the cortex involves the axon chemorepellant proteins semaphorin 3A and semaphorin 3F. Migrating neurons express neuropilins (receptors for semaphorins), and semaphorin 3A and 3F are expressed in the striatum, the region the neuroblasts must circumnavigate to reach the cortex (*13*).

During development, a secondary proliferative zone is formed along the third ventricle of the forebrain. This progenitor zone, known as the subventricular zone (SVZ), persists in the adult, where it continues to generate neurons. The subventricular zone, once thought to provide glia to the overlying cortex late in development, is now realized to provide a steady supply of new GABAergic neurons destined for the olfactory bulb; these neurons travel from the SVZ to the olfactory bulb in the rostral migratory stream. These cells continue to proliferate as they migrate in a posterior to anterior direction to populate the olfactory bulb (*14*, *15*). Cells within this stream undergo an unusual mode of cell migration, namely, as a chain of neurons ensheathed by a protective layer of glial cells (*16*). Two classes of molecules guide the migration of SVZ cells to the olfactory bulb. Polysialated neural cell adhesion molecule (N-CAM) provides a positive guidance cue on the cell surface of migrating neurons as loss of polysialated N-CAM by targeted gene disruption or by enzymatic digestion disrupts SVZ neuroblast migration (*13*, *17*). Two proteins involved in axon guidance serve as repellants for SVZ neuroblasts. The receptor tyrosine kinases EphB1-3 and EphA4 and their transmembrane ligands ephrins-B2/3 are expressed by SVZ neuroblasts. Infusion of the ectodomain of EphB2 or of ephrinB2 into the lateral ventricle disrupts migration, suggesting a role for Eph/ephrin signaling in migration (*18*). Diffusible signals also appear to guide SVZ neuroblast migration as a gradient of the axon guidance protein Slit repels the stream of migrating cells from the overlying striatum (*19*). Great interest has arisen concerning this cell population, because it continues to generate new neurons after birth, well into adulthood, providing a supply of new GABAergic neurons for the olfactory bulb and a population of partially committed stem cells that can be differentiated into interneurons when transplanted into the septum, thalamus, hypothalamus, and midbrain of embryonic brain (*20*).

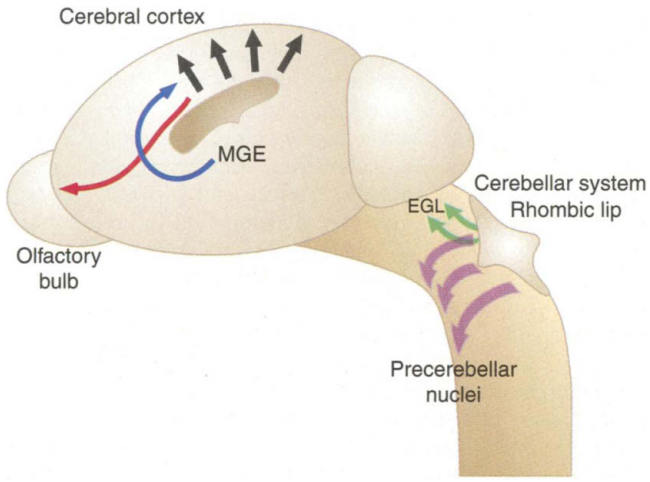

Fig. 2. DV and AP migratory pathways in vertebrate CNS migrations. Progenitors of the cerebellum arise along the rhombic lip at the midbrain/hindbrain junction and migrate dorsally, by repulsion to netrin1 and attraction to slit2 (green arrows). Progenitors of the precerebellar nuclei in the brainstem arise from more caudal portions of the rhombic lip and migrate ventrally along a netrin1 pathway (purple arrows). In the forebrain, cells from the MGE migrate dorsally into the cortex (blue arrow), while those of the rostral migratory stream follow a posterior to anterior trajectory (red arrow). A new migratory pathway emerges in higher vertebrates, namely, a radial pathway (black arrows).

Radial Migrations in Vertebrates

Before the cells migrating from the ventral forebrain arrive, the cerebral cortex begins to develop a radial migration pattern unique to higher vertebrates. The radial pathway of migration uses the processes of radial glial cells as a guide, and, importantly, provides a pathway for postmitotic neuronal migration. DV migrations, by contrast, generally involve mitotic neural precursor cells and do not use a glial scaffold. The initial hypothesis of glial guidance formed the basis for the radial unit hypothesis, which proposed that clones of cells generated in the VZ would be projected along radial glia into a columnar arrangement (*21*). This view was modified by studies on clonal dispersion in cortex, which showed widespread dispersion of some clones, and by imaging studies that showed tangential movements of some precursors (*22*, *23*). These two views have been clarified by recent findings, discussed above, that a large population of cortical interneurons arrive by a ventral to dorsal pathway of migration, from the MGE into the layers of cortex. Those cells that are widely dispersed cells from their subventricular origin are now thought to be interneurons (*24*, *25*). Cells that follow a simple radial pathway form the large output neurons of the cerebral cortex, the pyramidal cells. In contrast, GABAergic interneurons use a DV migration from the basal forebrain followed by a tangential movement into the forming layers of the cortex.

The initial movement of cells from the cortical germinal zone, on about embryonic day 11 or 12 in the mouse, generates a layer of postmitotic cells called the preplate, which is composed of Cajal-Retzius and subplate cells. As more cells exit the cell cycle and migrate through this region, they split this early zone into the outer layer of Cajal-Retzius cells and the underlying subplate forming the cortical plate. Sequential populations of cells migrate past the subplate to a position just underneath the Cajal-Retzius cells. The Cajal-Retzius cells form layer 1 and cells of the cortical plate generate layers 2 to 6. The cells within layer 6 are the earliest born neurons and those of layers 5 to 2 are sequentially later born cells, thus generating the "inside-out" arrangement described by Sidman (Fig. 3). A key insight into radial migration came from studies of the neurological mutant mouse *reeler*, which reels and stumbles from awkward coordination systems and has a cerebral and cerebellar cortex where the general pattern of neuronal layers is scrambled. Cloning of the *reelin* gene by insertional mutagenesis into the locus responsible for lamination defects in the *reeler* mutant mouse (*26*) revealed that the gene is responsible for the formation of the cortical plate, the backbone on which the neural layers are built. Reelin is a large extracellular matrix molecule, apparently synthesized by the earliest generated neurons, which binds to one of several receptor classes including VLDLR and ApoER2 (*26*, *27*). The binding of Reelin to receptors on adjacent neurons leads to a tyrosine kinase cascade that inludes phorphorylation of Dab1, an intracellular adapter protein the loss of which causes cortical malformations that resemble those in the *reeler* mouse. In *reeler*, those earliest generated cells fail to invade the preplate, thus failing to form a cortical plate with its systematic layering of cells. Expression studies indicate that the Cajal-Retzius cells, the cells of layer 1, express high amounts of Reelin and thus are the likely site of neuronal repulsion to form the underlying lamina. Thus, the Reelin pathway governs the overall patterning of cortical neurons into layers.

Mode of Movement of Immature Neurons Along Glial Fibers

The mode of movement of neurons along glial fibers, first proposed from static Golgi images, and then provided in detail from enhanced video microscopy, provides a framework for a series of genetic studies on the mechanism of cortical malformations (*28*). Here, the migration of the cerebellar granule cell has served as a paradigm for radial migration, because these cells can be purified in large numbers and used in cell-based assays of migration. Video microscopy of granule neurons first demonstrated the movement of neurons along glial fibers (*29*). Movement occurs in a salutatory cadence by formation of an adhesion junction along the length of the soma and the extension of a leading process, which projects short filopodia along the glial fiber (Fig. 4). Dynamic studies, labeling the membranes of migrating cells, showed rapid extension and retraction of this leading process over the length of the glial fiber. A critical aspect of migration concerns the cytoskeletal organization of the cells. Microtubules generate a "cage" around the nucleus (*30*) and apparently hold it in a caudal position as the cell moves. In addition, a centrosome or basal body projects a system of microtubules into the leading process. NudEL, a homolog of an *Aspergillus nidulans* gene involved in nuclear translocation, appears to localize to this structure (*31*). By video microscopy, vesicles move along this microtubule system; a cessation of vesicle movement accompanies a halt of migration. In contrast to growth cones, the microtubules seen in the leading process extend to the tip of the process. The only form of actin detected is cortical actin, a ring of which is seen in the cell soma. "Stress fibers," typical of extending growth cones, are not present in the leading process of migrating neurons. The importance of the cytoskeletal organization of migrating cells to movement is evident, because disruption of the system with pharmacologic agents halts migration. Thus, the mode of movement of neurons migrating on glial fibers is distinct from the mode of growth cone motility seen in axon extension. Indeed, the leading process of a neuron migrating along a glial process resembles a dendritic process more than it does an axon, a fact first noted by Ramon y Cajal (*32*).

In addition to revealing the cytoskeletal organization of migrating neurons, cell-based assays also proved useful in identifying *astrotactin* (*Astn1*), a gene that encodes a neuron-glial adhesion molecule. *Astn1* is expressed by neurons migrating along glial fibers in both cerebellum and cerebral cortex. A loss of *Astn1*, by targeted gene disruption, leads to a slowing of migration and to defects in the dendritic arborization of the target cell of the granule neuron, the Purkinje neuron (*33*, *34*). The disruption of Purkinje cell dendrite formation seen in mice lacking *Astn1* suggests that the slowed movement of the granule neurons, the presynaptic target cell of the Purkinje neuron, into position may provide an important timing device for dendritic development. Several other genes have been shown to function in glia-guided migration. These include neuregulin, which binds to ErbB4 on the glial surface and provides signals that maintain glial process formation (*35*, *36*). Although ASTN1 and neuregulin are expressed in postmitotic granule cell progenitors just before their migration along glial fibers, it is possible that even earlier genes act to set up the process of migration. In *C. elegans*, a number of genes act to disrupt axon formation. Homologs of one of these, *unc-51*, are expressed just after the cells leave the cell cycle, yet before they express markers of axon extension (TAG1) or neuron-glial binding (ASTN1). Unc51.1/Unc51.2 are serine-threonine kinases that provide a signaling casade for process formation in granule neurons (*37*). In *C. elegans*, *unc-51* mutants show a failure of axon outgrowth and of axon guidance, suggesting a role for this class of gene in steps required for cells to form migratory processes.

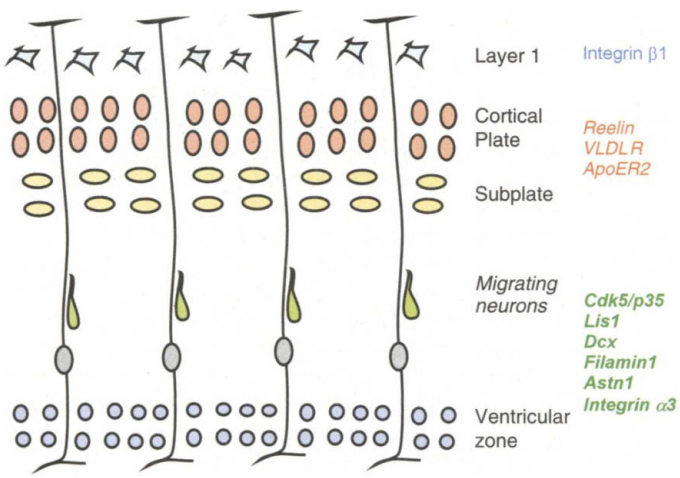

Fig. 3. Formation of the neuronal layers of cerebral cortex. The first-generated cells form layer 1 (Cajal-Retzius cells, blue), which later secrete Reelin. Thereafter, postmitotic cells migrate along the radial glial system to form the cortical plate (orange) and subplate (yellow) via the *reelin* pathway. As more cells arrive, the cortical plate generates a systematic set of layers (5 to 2). These later cells migrate along the radial glia (green) using genes that provide components of the cytoskeleton (*Lis1*, *Dcx*, *Filamin1*, and *Cdk5/p35*) or neuron-glia binding (*Astn1*, and *Integrin* α*3*). Continued cell division in the ventricular zone (blue) generates the most superficial layers.

Human Cortical Malformations

Studies on human cortical malformations (*28*, *38*) have described a series of neuronal migration syndromes, likely caused by disruptions in the cytoskeleton. Lissencephaly, a condition caused by less than normal sulcation of the cortex and thickening of the gray matter, is a large family of diseases. The range of malformations overlaps with two other syndromes, double cortex (DCX) and subcortical band heterotopias (SBH). The gene that is mutated in a severe form of Lissencephaly called Miller-Dieker syndrome is *Lis1*, which normally encodes a protein that binds to microtubules (*31*, *39*, *40*). Homozygous gene disruptions of *Lis1* result in lethality during embryogenesis. Heterozygotes survive but show defects in cell migration. Interestingly, the *Lis1*(+/–) cortex is not inverted, as seen in the *reeler* mouse phenotype; instead, migration appears to be slowed. Biochemical studies on the LIS1 protein show that it binds microtubules, suggesting that it may stabilize the microtubule network during cell migration. Attention has focused on the hypothesis that LIS1 also binds several NudEL homologs to regulate dynein function in the migrating neuron (*31*, *41*–*43*). This is consistent with the discovery of a *Drosophila Dlis1* gene mutation that results in defects in nuclear migration and in dendrite formation (*44*, *45*). Cdk5 phosphorylates NUDEL, suggesting that dynein motors are important in migration. Imaging studies from in vitro preparations, slice preparations, and electron microscopy studies all emphasize the posterior localization of the nucleus in neurons migrating along glia (*29*, *30*, *46*–*49*). Along with Miller-Dieker syndrome, XLIS is a common syndrome of classical lissencephaly in hemizygous males and DC/SBH is seen in heterozygous females. The Doublecortin gene *Dcx* encodes Doublecortin, another tubulin binding protein (*38*, *43*). DCX is ubiquitously expressed in developing neurons and exists both bound to the tubulin structures and cytoplasmic forms. In the search for proteins related to Doublecortin, a Doublecortin kinase was discovered. A mutant form of a related gene, *zyg-8*, has been reported in *C. elegans*, making it likely that *zyg-8* is the ancestral gene for Doublecortin (*50*). None of the genes that function in radial migration of postmitotic neurons appears to function in axon guidance. This contrasts with the migration of neuroblasts along the DV and AP (tangential) axes where the axon guidance systems Netrin1/UNC6,

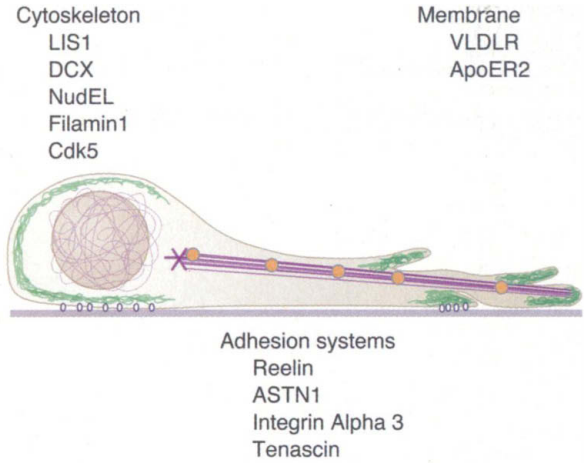

Fig. 4. Locomotion of the neuron along the glial guide. Neurons move along the glial guide in a salutatory motion, forming migrating junctions beneath the cell soma and at the tips of filopodia. Tubulin (purple) is organized into a cage surrounding the nucleus and a basal body (purple star) projects microtubules into the leading process. The latter extends short filopodia that enwrap the glial fiber as the cell moves. A ring of cortical actin (green) forms in the soma, with cortical actin seen along the distance of the leading process and extending into filopodia. As the cell moves, the nucleus remains in the posterior aspect and vesicles (orange) flow along the microtubule system.

Eph/ephrins, Semaphorin/neuropilin, and Slit play prominent roles in guiding migration.

Periventricular heterotopias highlight the function of actin binding proteins in migration. Individuals affected with periventricular heterotopias have pockets of ectopic cells lining the ventricles of the cortex. The gene mutated in this disorder, *filamin1*, encodes a protein that normally binds to actin and may be involved in the extension of filopodia as the cell moves along the glial fiber (*43*). Integrin α3, which could also act via actin filaments, appears to function in this step of migration as well (*51*). In mice, the Cdk5 kinase and its activator p35 induce actin reorganization when overexpressed in fibroblasts (*52*). Cdk5 modulates PAK kinases, effectors of the small guanosine triphosphatase (GTPase) Rac. Because PAK and Rho GTPases are implicated in actin reorganization, it may be critical for the dynamic aspects of the leading process of neurons migrating along radial glia. In mice lacking Cdk5 and p35, disruptions in cortical layering occur (*52*, *53*). Unlike the Reelin mechanism, which inverts layers, a loss of the Cdk5 pathway appears to affect later migrating neurons as the cortical layers emerge from the cortical plate (*52*). New evidence indicates that *cdk5* is regulated, at least in part, by the class III POU transcription factors *Brn-1* and *Brn-2*. *Brn-1*, which is expressed in the cortex, apparently functions via regulation of p35, an activator of Cdk5. A loss of *Brn-1* results in a delayed migration to layers 2 and 3 in the mouse. This result resembles the phenotype of mice lacking Cdk5 and p35 and suggests a role for these genes in the locomotion of cells along the glial fiber system (*54*). In *C. elegans*, several mutations have been identified in Ras-like GTPases, which would be expected to remodel the actin cytoskeleton as in the formation of the leading process and its filopodia. These include *unc-73* and *mig-2*, protein products of which control the speed of migration in worm neurons. New families of genes involved in migration are therefore likely to come from a clearer understanding of the basic cell biology of migration, especially of signaling cascades critical for the specialized cytoskeletal assemblies seen in migrating neurons.

Conclusions

Vertebrates show far more widespread neural migrations than previously realized. In general, these migrations can be seen as DV or AP migrations, pathways thought to be prominent in lower organisms but not in vertebrates. Indeed, genes discovered in *C. elegans* and *Drosophila* provide molecular mechanisms for the DV and AP migrations in higher vertebrates. In the systems studied so far, these genes encode proteins that direct axon guidance in spinal cord and visual systems, and neuroblast migrations in the cerebellar system, the MGE/cortical system, and the rostral migratory stream. Genes for the radial pathway of migration have been cloned by the analysis of neurological mutant mice (Reelin pathway) and of humans with cortical malformations (*Lis1*, *Dcx*, and *Filamin1*). None of these genes has been shown to play a role in axon guidance. Model systems, with either cell-based assays (granule cells) or tissue slice preparations (cerebral cortex) identify many of the genes for radial migration as cytoskeletal or neuron-glia adhesion ligands (*Astn1*). Future experiments on the genetics of neuronal migration in invertebrates and vertebrates will reveal the scaffolds for CNS neuronal migrations. As the molecular basis of migratory pathways becomes more clear, we should begin to discern the underlying benefit of vast movements of cells to the development of the circuitry of the brain.

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