Environmental Medicine, Vol. 46 No.1, 2, 2002 (page 7 ~ 15) **Review Article**

# Neuronal Migration and Neuronal Migration Disorder in Cerebral Cortex

Xue-Zhi SUN,[1,2] Sentaro TAKAHASHI,[2] Chun CUI,[3] Rui ZHANG[3]
Kazuo KOGA,[1] Minoru INOUYE[4] and Yoshiharu MURATA[5]
[1] Space Medicine Research Center
Research Institute of Environmental Medicine
Nagoya University, Nagoya 464-8601, Japan
[2] Environmental and Toxicological Sciences Research Group
National Institute of Radiological Sciences, Chiba 263-8555, Japan
[3] Department of Anatomy and Developmental Neurobiology
School of Medicine, Tokushima University, Tokushima 770-8503, Japan
[4] Shin Nippon Biomedical Laboratories, Ltd.
2438 Miyanoura, Yoshida, Kagoshima 891-1394, Japan
[5] Department of Teratology and Genetics
Research Institute of Environmental Medicine
Nagoya University, Nagoya 464-8601, Japan

**Abstract:** Neuronal cell migration is one of the most significant features during cortical development. After final mitosis, neurons migrate from the ventricular zone into the cortical plate, and then establish neuronal lamina and settle onto the outermost layer, forming an "inside-out" gradient of maturation. Neuronal migration is guided by radial glial fibers and also needs proper receptors, ligands, and other unknown extracellular factors, requests local signaling (e.g. some emitted by the Cajal-Retzius cells of the marginal zone) to stop neuronal migration. This process is highly sensitive to various physical, chemical and biological agents as well as to genetic mutations. Any disturbance of the normal process may result in neuronal migration disorder. Such neuronal migration disorder is believed as major cause of both gross brain malformation and more special cerebral structural and functional abnormalities in experimental animals and in humans. A number of instructive studies on nongenetic models (e.g. MAM- or irradiation-treated rodents) and mutations (e.g. Reelin- or Tish-mutant animals) have established the foundation of cortex formation and provided a framework in which to understand mutants of cortex development. The recent studies on several genetic model systems of neuronal migration disorder provide further insight into the development pathways that underlie normal and abnormal neuronal migration.

**Key words:** cell migration, cerebrum, heterotopic mass, radial glial cell, ventricular zone

The cerebral cortex, which is by far the largest part of the mammalian brain, is divided into distinct areas that were defined originally in terms of their cytological differences and were later discovered to serve different functions. All areas of the cortex have a similar basic organization, with neurons arranged in six layers.[1] The layering is produced by variations in the densities and sizes of cell bodies through the cortical depth. All neuronal cells (with few exceptions) are generated the surface of the embryonic cerebral ventricles at sites far from their ultimate positions in the adult mammalian brain.[2,3] Neuronal migration is necessary and an essential step in the genesis of the nervous system, particularly in laminated brain regions.[4-8] By this migrating process many billions of newly generated neural cells are addressed to their proper position mainly in nuclear masses or in the cerebral and cerebellar cortexes. General or topical loss of control over this process is generally called abnormal neuronal migration or neuronal migration disorder. Neuronal migration disorder will result in either cell death or improper positioning of functional cell groups. This in turn will result in failing connections or improper wiring (misconnection) responsible for functional deficiencies and epilepsy. Abnormal migration had been linked to congnitive deficits, mental retardation, and motor disorders.[9-13] This review focuses on the normal cellular processes of neuronal migration, disruptions in such processes give rise to several disorders of brain development, and recent advances in our understanding of the molecular mechanisms of neuronal migration disorder.

## Neuronal Migration in the Cerebral Cortex

### *Patterns of neuronal migration in the cerebral cortex*

Neurons in the cerebral cortex are born in a region of proliferating cells called the ventricular zone, which lines the lateral ventricle of each telencephalic hemisphere. The ventricular zone of the telencephalon provides the neuronal and glial stem cells.[2,3,14-16,19,25] After completing their final mitotic division, cortical neurons engage into a long migration with

Reprint requests to: Dr. Xue-Zhi SUN, Environmental and Toxicological Sciences Research Group, National Institute of Radiological Sciences, Chiba 263-8555, Japan. Tel: 043-206-3159 Fax: 043-2514853 E-mail: sun_s@nirs.go.jp

radial centrifugal fashion through the intermediated zone (future white matter) toward the cortical plate where they settle and differentiate.[26] Neuronal migration in the neocotex takes place for the greater part between the 8th and the 20th weeks of gestation in humans,[18] and between embryonic day 14 (E14) and postnatal day 5 (P5) in rats.[21] The migration of young neurons is guided from an early stage by a system of radial glial fibers that span the width of the thickening telecephalon.[17-20] Radial glias are bipolar cells with one short process extended to the adjacent ventricular surface and a second projecting to the pial surface. The perikarya of the radial glial cells are in the ventricular and subventricular zones.[22-24,27,28] As a rule, it has been suggested that neurons of layer I, the giant Cajal-Retzius neurons and layer VIb, the lower part of layer VI are laid down as a single neuronal network, the primordial plexiform layer.[29,30,35-38,43] This primordial plexiform layer is thought to provide a cytoskeleton for the successive neuronal migration waves as these become sandwiched between the upper and the lower part of the lower part of cerebral structure (Fig. 1). The six layers of the neocortex are generated in an inside to outside sequence, e.g. layer III neurons arriving before layer II neurons which means that later migration waves have to pass earlier migration waves.[41,42]

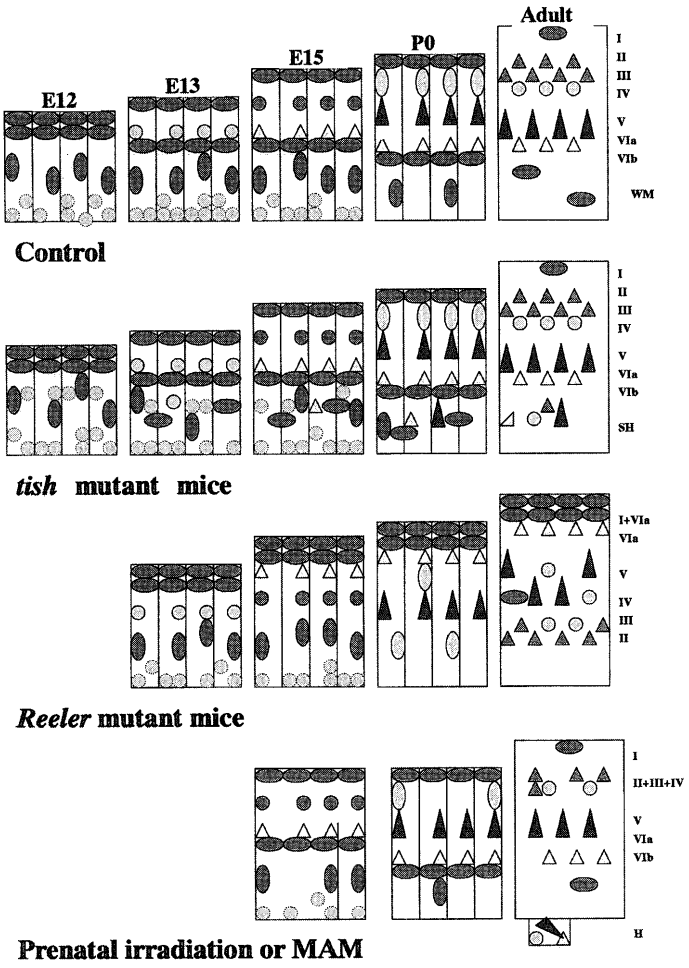


Fig. 1 Schemic representation of cortical development in three current rodent models of neuronal migration disorder from embryonic day (E) 12, 13, 15, postnatal day 0 (P0) to adult age.
Experiment rats for nongenetic models are treated on E14-15 with methylazoxymethanol (MAM) or irradiation. Three models (*tish* mutant rat, *reeler* and *reeler*-like mutant mouse and the prenatal irradiation- or MAM-treated rat) show that neuronal migration disorders can result from an abnormal neurogenesis (*tish*), a failure of preplate splitting (*reeler*) or a lesion of radial glia cells (X-ray, MAM). WM: white matter, SH: subcortical band heterotopia, H: heterotopia.

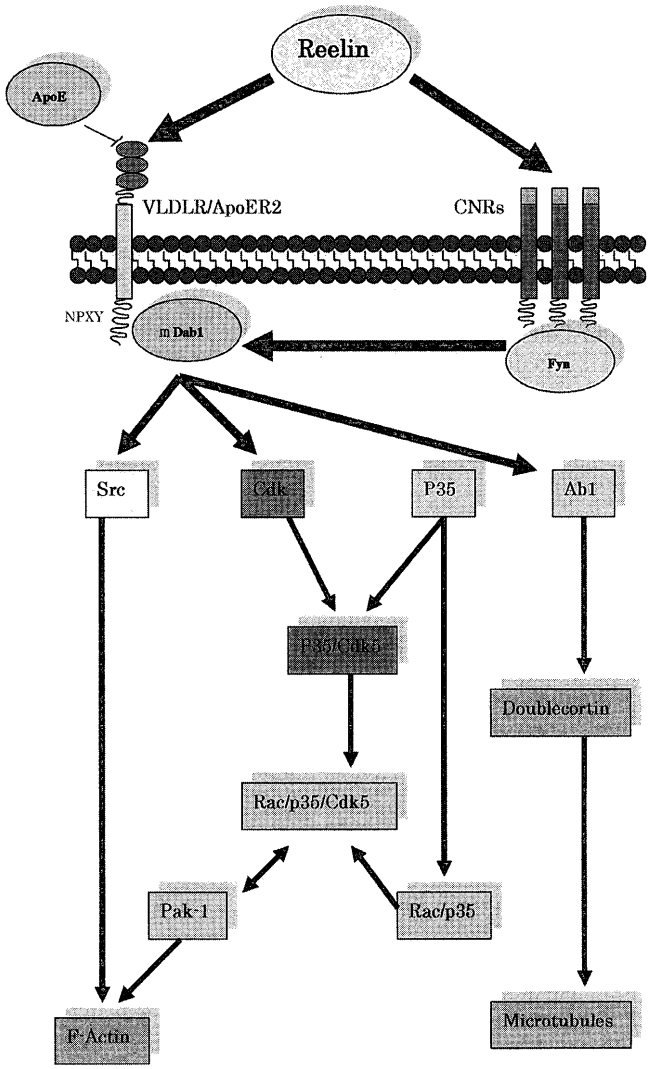


Fig. 2 Schema summarizing Reelin signaling pathway.
Reelin is expressed by Cajal-Retzius cell in cortical layer I and binds the cadherin-related receptors (CNRs) and the VLDL receptor or ApoE receptor-2, or both. CNR binding initiates phosphorylation of a Scr family kinase, possibly Fyn, which is considered to phosphorylate mDab-1 associated with VLDLR/ApoER2. Reelin binding to VLDLR and ApoER2 also appears to result in phosphorylation of mDab-1 through kinase domains in the cytoplasmic region of the receptors. Activated mDab-1 is then though to interact with Cdk5, Src, and Ab1 to regulate cyotskeletal remodeling, directly or indirectly.

***Stop of migration in the appropriate cerebral layer***

Cell migration into the cortical plate must also stop at the appropriate location. This choice point and determining this point is essential for normal cerebral cortical development. The process of the end of neuronal migration involves the detachment from the radial glial fibers triggered by local signals (Fig. 2),[32,35,46,47] some of them emitted by the Cajal-Retzius cells of the marginal zone.[29,43]

Insights into the mechanisms governing how cells know when to stop have begun to be elucidated through the analysis of several mouse mutants. In particular, the characterization of the Reeler mouse mutant provided the first insights into the process of laminar organization. The Reeler mouse was first identified as a postnatal behavioral defect,[44] and the neuropathological studies have showed that the cortical layering pattern is just opposite from the normal inside to outside migrating pattern.[45,48,49] It has been known that Reelin is pressed by Cajal-Retzius cells in layer I.[31,33,34] As one of extracellular matrix molecule, Reelin plays a role to form a Reelin's zone to stop migration of the earliest generated neurons in the cerebral cortex (detail description see below). However, Cajal-Retzius cells in the Reeler mice were found to be remained at the top of the undivided preplate, or superplate. These heterotopic Cajal-Retzius cells are thought to be the reason to form the inverted cortical layering in the Reeler mutant mouse (Fig. 1).

## Neuronal Migration Disorder Induced by Teratogenic, Physical and Biological Influences

The process of neuronal migration involves three main steps: (a) commitment to a specific cortical layer, (b) migration proper and (c) stop of migration in the appropriate layer. These three steps are under different control mechanisms. This process also requires known receptors and ligands such as astrotactin, and extracellular matrix molecules and their cell surface receptors. Once these components are blocked, neuronal migration will be prevented or become slow. It is not surprising that migration can be disturbed by teratogenic, physical and biological influences that occur during the period of migration.

The use of teratogenic (e.g. alcohol or cocaine),[50-52,59,115] physical (e.g. irradiation, heat)[53-57] and biological (e.g. viral infection)[58] agents has provided animal models for studying neuronal migration disorder. A large number of animal experiments involving different species and different protocols of exposure these agents to the potentially damaging effects on the neuronal migration of the cerebral cortex have been carried out. These nongenetic model have been generated by exposure of pregnant females during the early period of migration to irradiation or toxic substances such as the antimitotic agent methylazoxymethanol (MAM),[60-62] cocaine[115] or ethanol.[50-52,59] Whatever their respective mechanisms, all these influences will lead neurons to differentiate in an abnormal heterotopic posi-

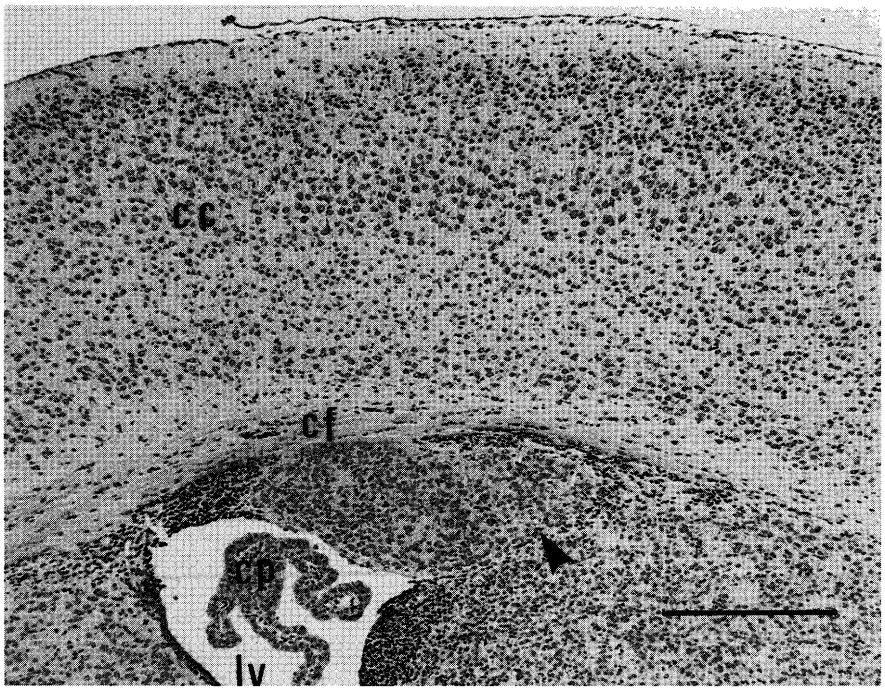


Fig. 3 An example of a typical heterotopica (arrowhead) located bellow the cerebral cortex (cc) of a 1-week-old mouse irradiated on embryonic day 13 (E13), which corresponds to E15 in the rat.[114]
Heterotopia is separated from the cerebral cortex by a band of fibers of corpus callosum (cf). cp: choroids, lv: lateral ventricle. Hematoxylin and eosin stain. Scale bar = 280 μm.

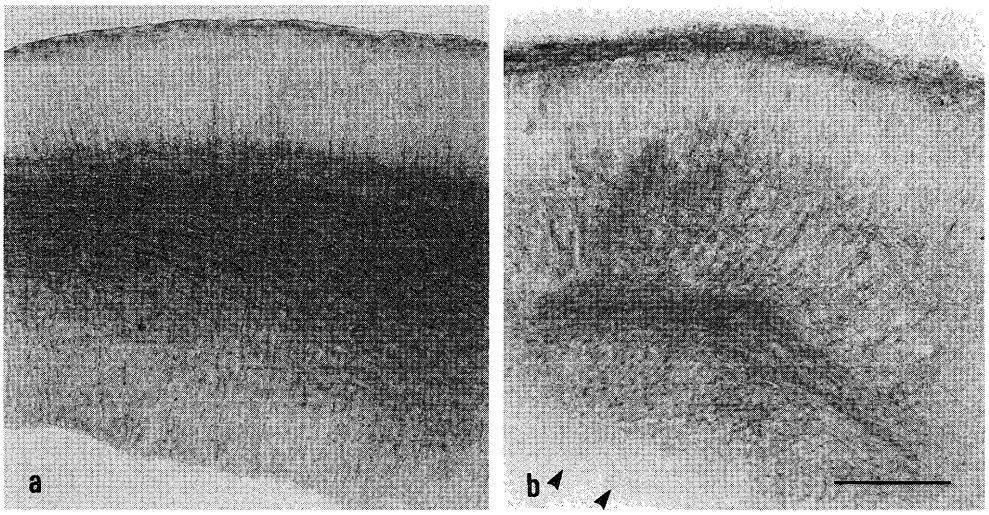


Fig. 4 An example of anti-Midkine (MK)-immunoreactive radial glial fibers in the mouse brain mantle on embryonic day 17.
**a**: radial glial fibers are straight and perpendicular to the pial surface in the control mouse. **b**: Radial glial fibers are crumpled and no longer regularly distributed to the pial surface in the mouse irradiated on embryonic day 13. Arrowheads indicate the place of ectopic masses. Scale bar = 125 μm.

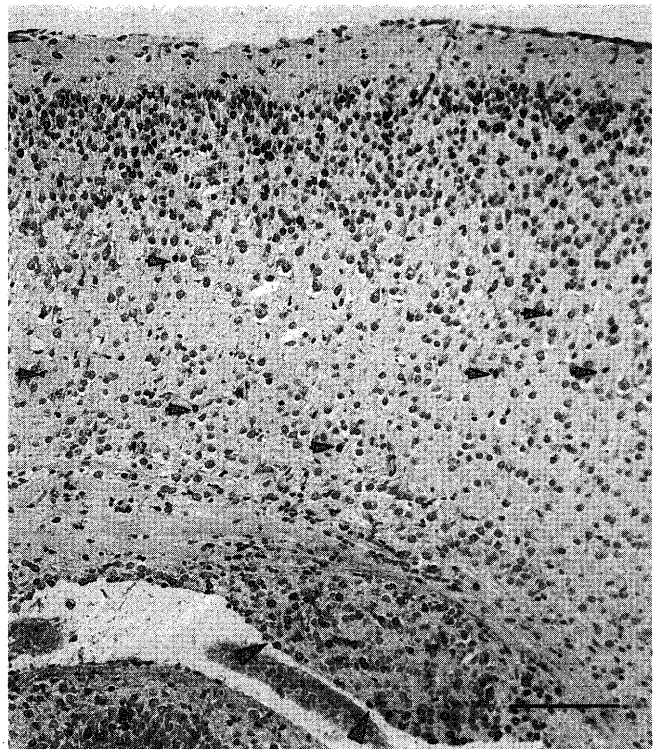

Fig. 5 An example of anti-bromodeoxyuridine (BrdU)-labeled young neurons migrated along disturbed pathways in a 1-week-old mouse irradiated on embryonic day 13.
Some of these neurons could not move far from the place of their origin around the lateral cerebral ventricle and remained in the lower inappropriate layer (arrows) or near the ventricle to form heterotopic cell mass (arrowheads). Scale bar = 110 μm.

tion. Absence, interruption or excessive migration will lead neurons to differentiate respectively in a subcortical (i.e. along the ventricle), intracortical (i.e. in the white matter or in an inappropriate layer) or extracortical (i.e. in the submeningeal space) position. Pregnant mice subjected to X-irradiation at a single dose of 1.5 Gy on embryonic day 13 which is the radiosensitive stage produced offspring with neuronal heterotopia located in enlarged lateral ventricles of the cerebral hemispheres (Fig. 3).[53,55,57,67] Midkine (MK) immunocytochemical staining[63-66] was carries out to confirm a course corresponded to the distribution of the radial glial fibers (neuronal pathway). These MK-staining fibers radially traversed the distance between the ventricular zone and the pial surface. They were straight and perpendicular to the pial surface, oriented in the direction of neuronal migration in the normal brain (Fig. 4a). However, in the brain of the irradiated mice, MK-staining radial glial fibers (examination from 6 hr after irradiation) were crumpled and no longer regularly distributed to the pial surface (Fig. 4b). It is well know that radial glial cells play a role as guides for migrating neurons.[54,57] When a large number of young neurons migrated along such a disturbed pathway, some of them could not move far from the place of their origin around the lateral cerebral ventricle and remained in the lower inappropriate layer or near the ventricle to form heterotopic cell mass (Fig. 5).

## Neuronal Migration in Neurological Mutant Mice

Studies on neurological mutant murine with brain malformation[68,69] provide a new approach to the discovery of genetic loci that contribute to neuronal migration in developing brain. Classical studies of mutants, Reeler, Scrambler, Yatari, have

been assumed to be models for neuronal migration in cerebral cortex. In Reeler mutant mice, the cortical layering appears inverted.[45,70] In other words, the first cells of definitive cortex to migrate out of the ventricular zone end up residing in the superficial cortical plate and subsequent cells migrate to and stop in progressively deeper positions. This migration pattern is opposite of the normal inside to outside development of the cerebral cortex. The affected gene in Reeler mice was found to encode for a large extracellular matrix protein named Reelin.[32,33,71,72] Reelin has homology to F-spondin and contains epidermal growth factor-like repeats similar to those of tenascin C, tenascin X, restrictin, and the integrin β chain.[33] Reelin is expressed by Cajal-Retzius cells and is found extracellularly in the molecular layer (layer I).[32,33,35] These data suggest that Reelin is required for the normal inside to outside positioning of cells as they migrate from the ventricular zone.[27,73] This was the first component of a signaling pathway guiding cells to the correct location in the cortex.

Because Reelin is an extracellular matrix molecule, a receptor for Reelin would be required for signaling to the migrating cells. Reelin signaling pathway was summarized in Fig. 2. Reelin has been found to bind to cadherin related receptor (CNRs),[74] at least two members of the LDL receptor family,[75-77] and α3β1-integrin.[78] Binding of Reelin to α3β1-integrin functions as a stop signal; however, the downstream components within the cell that regulate the migration stop are not known. Upon contact with Reelin, the CNRs initiates phosphorylation of the cytoplasmic second messenger mDab1, possibly through a CNR-associated tyrosine kinase Fyn[74] or through the LDL receptor.[76,77] The scrambler and Yotari mutant mice have been identified as mutations in the mDab1 gene.[10] Scramber, Yotari, and mDab1-/- all show a Reeler phenotype further supporting the notion that they lie the same pathway. Phosphorylated mDab1 can interact with a variety of proteins including the SH2 domain of Src.[79] Src has been shown to interact with actin and affect cytoskeletal remodeling.[80-82] Src-deficient cells exhibit strong adhesion to surfaces and low migration capacity.[83] Therefore, these data tie Reelin signaling pathway to cell migration and enable neurons to be targeted to the appropriate layer of the cortex. mDab1 also activates the proto-oncogene c-Ab1. Once activated, c-Ab1 can phosphorylate Cdk5, a process that is enhanced by Cable, thus activating Cdk5.[84] Cdk5 and p35 (another activator of Cdk5) have also been implicated in directing neurons to the appropriate location within the cerebral cortex.[85-87] Both are highly expressed in the developing central nervous system and mice engineered to be homozygous mutant for Cdk5 or p35 also show a cortical defect similar, although not identical, to the Reeler phenotype.[85] Nikolic et al have shown co-localization of Cdk5, p53, Rac and Pak-1 in neurons.[88] They suggest that a Rac-dependent hyperphosphorylation of Pak-1 results in a dynamic down-regulation of actin polymerization and enhancement of new focal complex formation during cell migration and process outgrowth.[88] Activation of Pak has also been shown to result in a loss of stress fibers and focal adhesions.[89] These data indicate that the Rac family of GTPases along with Scr family members can regulate cytoskeletal remodeling and therefore transduce guidance signals from the cell membrane to the cytoskeleton.

## Human Migration Disorders and Cortical Malformation

The genes mutated in several human disorders of neuronal migration also provided a basis for linking the cytoskeleton to neuronal migration. In man, more than 25 syndromes with neuronal migration disorders have been described.[39] Neuronal migration disorders primarily affect development of the cerebral cortex, but the extent and nature of the cortical malformation varies greatly.[40] Table 1 summarized genetics of neuronal migration, characteristics of the pathologic alterations and underlying defect in some of these syndromes both in mutant rodent models and humans. It can provide important insights into the histogenesis of the cerebral cortex and the molecular etiology for the cerebral malformations.

Lissencephaly represents a broad class of neuronal migration disorders. It can be described as a brain with a macroscopically smooth cortical surface in which a more or less layered cortex can be observed on microscopical examination. It occurs as an isolated abnormality (isolated lissencephaly sequence) or in association with dysmorphic facial appearance in patients with Miller-Dieker lissencephaly.[90] These abnormalities have been attributed to defects in neuronal migration.[91] A hemizygous chromosomal deletion at band 17p13.3 led to identification of lissencephaly-1 (LIS-1) as the causative gene in this anomaly. The LIS-1 gene codes for the LIS1 protein, which contains eight WD-40 repeats of the type found in G-protein β subunits. It is a regulatory subunit of brain intracellular Platelet-Activating-Factor acetyllhydrolase (PAFAH1B1),[92] a G-protein-like trimer that regulates cellular levels of the lipid messenger PAF.[93] The importance of PAFAH1B1 in the developing brain is supported by the high-level expression of mRNA transcripts for all three subunits during neuronal migratory epochs in cerebrum. The LIS-1 gene product is prominent in Cajal-Retzius cells and ventricular neuroepithelium in developing human cortex.[94] How the absence of the LIS-1 gene product affects PAF-AH1B1 function, PAF signaling in the cell, and ultimately neuronal migration remains to be understood. In addition, LIS-1 may have ad yet unidentified interactions in the cell, as suggested by the ability of the WD-40 repeat segments of LIS-1 to interact with the cytoskeketon. The normal gene product of LIS1 is widely distributed in the grey and white matter of the brain and spinal cord in controls. It has been found both in neurons

Table 1 Genes implicated in neuronal migration disorder

| Mutation | Symbol | Chromosome | Position | Description | Source (No. of references) |
|---|---|---|---|---|---|
| **Mice** | | | | | |
| Reeler | *rl* | 5 | 8.0cM | Migration arrest in early development with subsequent failure of cortical plate formation. Reeler encodes a large ECM molecule produced by Cajal Retzius cells in the molecular layer. | 32, 108, 109. |
| Scrambler | *scr* | 4 | 49.7cM | Phenotype is identical to that of reeler. Scrambler is a mutation in a disabled gene that encodes a phosphoprotein that binds nonreceptor tyrosine kinases. | 110, 111. |
| Yotari | *yot* | 4 | 49.7cM | Allele of scrambler. | 112, 113. |
| Disabled | *mdabl* | 4 | 49.7 cM | Allele of scrambler. | 113. |
| Lissencephaly | *Lis1* | ND | ND | Failure of forebrain neuronal migration via deletion of th ebeta subunit of platelet activating factor acetylhydrolase (PAFAH1B1, also known as Lis1) | 109. |
| Zellweger | *PEX1, PEX2* | ND | ND | Failure of forebrain neuronal migration via defective peroxisomal biogenesis. | 106, 107. |
| **Rats** | | | | | |
| Double cortex | *tish* | ND | ND | Cortical neurons are seen in a bilateral heterotopia that is prominent below the frontal and parietal neocortex; heterotopoas rare beneath the temporal cortex. | 116. |
| **Humans** | | | | | |
| MD syndrome | LIS1 | 17 | 17p13.3 | A class of spontaneous and inherited disorders (MD) with failure of migration in forebrain, fewer gyri, and smoother gyri in cerebral cortex. In a murine model, the mechanism involves the deletion of the beta-subunit of platelet activating factor acetyldehydrogenase (PAFAH1B1). | 117. |
| Lessencephaly | LIS | | | Subset of MD with failure of migration in forebrain. Individuals that express the gene have a smooth brain, i.e. fewer gyri in the cerebral cortex. | 118. |
| X-Linked Lessencephaly | xLIS | X | Xq22.3-q23 | Males show lissencephalic phenotype. Females have a double cortex phenotype with disorganized forebrain gray matter and an extra layer of cells located underneath the white matter. The defective gene encodes the doublecortin protein. Doublecortin is homologous to the amino terminus of a predicted protein kinase, which suggests a role for signal transduction. | 97, 98, 99. |
| Zellweger syndrome | At least 10 genes proposed | ND | ND | Failure of cortical migration, neuronal laminae do not form. In two murine models, the molecular mechanism involves defects in the PEX2 or PEX5 genes, both genes required for neuronal peroxisomal biogenesis. | 117. |
| Bilateral Periventricular Nodular band Heterotopias | BPNH | X | Xq28 | Forebrain neurons form heterotopias in the subependymal zone. The cellular mechanism is unknown. | 101, 102, 119. |
| Microencephaly | ND | 1 | 1q25 | A class of disorders resulting in reduced brain size due to smaller neuronal lamina. The pattern of lamination is normal; the thickness of the layers is reduced. (Nor involving head structures.) One subgroup of families has been mapped. | |

ECM: extracellular matrix, EGF:epithelial growth factor, ND: not determined, MD: miller-Dieker.

and in glial cells.[95] Prenatal diagnosis of the chromosome band 17p 13.3 deletion is now possible using Fluorescent In Situ Hybridization (FISH) and Fragment Restriction Length Polymorphism (FRLP) techniques after chorionic villus biopsy sampling.

Another group of disorders with this general class of neuronal migration disorder is X-linked.[91] The first X-linked malformation syndrome is X-linked LIS. In X-LIS, hemizygous males have lissencephaly and heterozygous females have subcortical band heterotopia that is also known as a double cortex (DC) syndrome. The clinical presentation in affected males is similar to that with classical lissencephaly and chromosome 17p13.3 deletion: profound mental retardation, epilepsy with multiple seizure types, feeding problem and a shortened life span. The female carriers have mental retardation, behavior problems and epilepsy. Linkage of DC/X-LIS to Xq21-24 was first demonstrated.[97,98] Subsequent positional cloning identified a novel gene named Doublecortin.[98,99] Doublecortin is a microtubule-associated protein which is expressed widely by migrating neurons.[13] It is often possible to predict this gene mutation from careful review of brain imaging studies: mutations of frontal gradient of lissencephaly, whereas mutations of X-LIS are associated with a frontal to occipital gradient.[100] The second X-linked malformation syndrome is bilateral periventricular nodular heterotopoa (BPNH) that consists of BPNH in females and prenatal lethality or a more severe phenotype in males. In this disorder, large neuronal masses of well-differentiated cortical neurons fill the adult subependymal zone. The syndrome is located at Xq28[101-103] the corresponding gene was identified as Filamin 1 (FLN1), which encodes an actin-cross-linking phosphoprotein which is required for movements of many cell types.[104]

Zellweger syndrome is a second broad class of cortical malformation, causing death within approximately six months of life.[96] Like lissencephaly, Zellweger patients have characteristic gryal abnormalities in the cerebral cortex, which show a stereotypic medial pachygyria (reduced number of gyri, but they are abnormally large) and lateral polymicrogyria (excess number of small gyri). This syndrome is a genetically heterogeneous disorder that may arise from defects on at least 10 different genes.[105] Recently, animal models for a human of Zellweger syndrome have provided by targeted deletion in mice of genes encoding the PEX2 35-kDa peroxisomal membrane protein[106] and the PEX5 peroxisomal protein import receptor.[107]

## Conclusion

Neuronal cell migration is a key event during cortical development. After their final mitosis, neurons migrate from the ventricular zone through the cell-sparse intermediate zone into the cortical plate. After entering the cortical plate, neuronal cells migrate through the established neuronal lamina and settle onto the outermost layer, forming an "inside-out" gradient of maturation, a process which is essential to cortical neuronal lamination. The process of neuronal cell migration is highly sensitive to various physical, chemical and biological agents as well as to genetic mutations. Disturbance of neuronal migrating pathway (radial glial fiber) or extracellular factors or correct settling of Cajal-Retzius cells is considered for all types of neuronal migration. Arrested or excessive migration will lead neurons to differentiate in a hetertopic position. Such neuronal migration disorder is believed as major cause of both gross brain malformation and more special cerebral structural and functional abnormalities in experimental animals and humans. A number of instructive studies on nongenetic models (e.g. MAM- or irradiation-treated rodents) and mutations (e.g. reelin- or tish-mutant animals) have established the foundation of cortex formation and provided a framework in which to understand mutants of cortex development. However, knowledge to understand the making of our brain is still very limited. For instance, how many receptors and ligands involve neuronal migration processes? how many genes regulate genetic disorders of neuronal migration? what are genetic mechanisms that act at the beginning of migration, during the onging process of migration and in several discrete steps at the completion of migration? It is clear that further research is needed to gain deeper insight into the genetic and molecular mechanisms underlying normal and abnormal neuronal migration.

## Acknowledgements

The authors are grateful to Ms. Kiyoko Suzuki and Ms. Yasuko Koto of Environmental and Toxicological Sciences Research Group, National Institute of Radiological Sciences for helping our in retrieval of scientific references for this review.

## References

1) Krieg WJS. Connections of the cerebral cortex. I. The albino rat. B. Structure of the cortical areas. J Comp Neurol 1946; 84: 277–324.
2) Shiman R, Rakic P. Neuronal migration, with special reference to developing human brain: A review. Brain Res 1973; 62: 1–35.
3) Rakic P. Cell migration and neuronal ectopias in the brain. In: Bergsma ed. In Birth Defects: Original Series. Liss, New York, 1975; 9: 95–129.
4) Marin-Padilla M. Early prenatal ontogenesis of the cerebral cortex (neocortex) of the *Felix domestica*. A Golgi study. I. The primordial neocortical organization. Z Anat Entwicklungsgesch 1971; 134: 117–145.
5) Marin-Padilla M. Cajal-Retzius cells and the development of the neocortex. Trends Neurosci 1998; 21: 64–71.
6) Rakic P. Specification of cerebral cortical areas. Science 1988; 241: 170–176.
7) Rakic P. Principles of neuronal cell migration. Experientia 1990; 46: 882–891.
8) Hatten ME. The role of migration in central nervous system neuronal development. Curr Opin Neurobiol 1993; 3: 38–44.
9) Eksioglu YZ, Scheffer IE, Cardenas P, et al. Periventricular heterotopia: An X-linked dominant epilepsy locus causing aberrant cerebral cortical development. Neuron 1996; 16: 77–87.
10) Bonneau D, Toutain A, Laquerriere A, et al. X-linked lissencephaly with absent corpus callosum and ambiguous genitalia (XLAG): clinical, magnetic resonance imaging, and neuropathological findings. Ann Neurol 2002; 51: 340–349.
11) Howell BW, Hawkes R, Soriano P, et al. Neuronal position in the developing brain is regulated by mouse disabled-1. Nature 1997; 389: 733–737.
12) des Portes V, Pinard JM, Billuart P, et al. A novel CNS gene required for neuronal migration and involved in X-linked subcortical laminar heterotopia and lissencephaly syndrome. Cell 1998; 92: 51–61.
13) Gleeson JG, Allen KM, Fox JW, et al. *doublecortin*, a brain-specific gene mutated in human X-linked lissencephaly and double cortex syndrome, encodes a putative signaling protein. Cell 1998; 92: 63–72.
14) Jacobson M. Developmental Neurobiology, Plenum Press, New York, 1978; 401–448.
15) McConnell SK, Kaznowski CE. Cell cycle dependence of laminar determination in developing neocortex. Science 1991; 254: 282–285.
16) McKay R. Stem cells in the central nervous system. Science 1997; 276: 66–71.
17) Rakic P. Mode of cell migration to the superficial layers of fetal monkey neocortex. J Comp Neurol 1972; 145: 61–83.
18) Sidman RL, Rakic P. Neuronal migration, with special reference to developing human brain: a review. Brain Res 1973; 62: 1–35.
19) Levitt P, Cooper ML, Rackic P. Coexistence of neuronal and glial precursor cells in the cerebral ventricular zone of the fetal monkey: an ultrastructural immunoperoxidase analysis. J Neurosci 1981; 1: 27–39.
20) Rakic P. Neuronal-glial interaction during brain development. Trends Neurosci 1981; 4: 184–187.
21) Raedler E, Raedler A, Feldhaus S. Dynamical aspects of neocortical histogenesis in the rat. Anat Embryol 1980; 158: 253–269.
22) Gadisseux JF, Evrard P. Glial-neuronal relationship in the developing central nervous system. Dev Neurosci 1985; 7: 12–32.
23) Levitt P, Cooper ML, Rakic P. Early divergence and changing proportions of neuronal and glial precursor cells in the primate cerebral ventricular zone. Dev Biol 1983; 96: 472–484.
24) Kadhim HJ, Gadisseux JF, Evrard P. Topographical and cytological evolution of the glial phase during prenatal development of the human brain: Histochemical and electron microscopic study. J Neuropathol Exp Neurol 1988; 47: 166–188.
25) Boulder Committee. Embryonic vertebrate central nervous system: revised terminology. Anat Rec 1970; 166: 257–262.
26) Shoukimas GM, Hinds JW. The development of the cerebral cortex in the embryonic mouse: an electron microscopic serial section analysis. J Comp Neurol 1978; 179: 795–830.
27) Hatten ME. Central nervous system neuronal migration. Annu Rev Neurosci 1999; 22: 511–539.
28) Bentivoglio M, Mazzarello P. The history of radial glia. Brain Res Bull 1999; 49: 305–315.
29) Super H. Soriano E, Uylings HBM. The functions of the preplate in development and evolution of the neocortex and hippocampus. Brain Res Rev 1998; 27: 40–64.
30) Meyer G, Goffinet AM. Prenatal development of *reelin*-immunoreactive neurons in the human neocortex. J Comp Neurol 1998; 397: 29–40.

31) Alcantara S, Ruiz M, D'Arcangelo G, et al. Regional and cellular patterns of *reelin* mRNA expression in the forebrain of the developing and adult mouse. J Neurosci 1998; 18: 7779–7799.
32) D'Arcangelo G, Miao GG, Chen SC, et al. A protein related to extracellular matrix proteins deleted in the mouse mutant reeler. Nature 1995; 374: 719–723.
33) D'Arcangelo G, Nakajima K, Miyata T, et al. Reelin is a secreted glycoprotein recognized by the CR-50 monoclonal antibody. J Neurosci 1997; 17: 23–31.
34) Schiffmann SN, Bernier B, Goffinet A. *reelin* mRNA expression during mouse brain development. Eur J Neurosci 1997; 9: 1055–1071.
35) Ogawa M, Miyata T, Nakajima K, et al. The *reeler* gene-associated antigen on Cajal-Retzius neurons is a crucial molecule for laminar organization of cortical neurons. Neuron 1995; 14: 899–912.
36) del Rio J, Martinez A, Fonseca M, et al. Glutamate-like immunoreactivity and fate of Cajal-Retzius cells in the murine cortex as identified with calretinin antibody. Cereb Cortex 1995; 5: 13–21.
37) Frotscher M. Cajal-Retzius cells, reelin, and the formation of layers. Curr Opin Neurobiol 1998; 8: 570–575.
38) Lambert de Rouvroit C, Goffinet AM. The reeler mouse as a model of brain development. Adv Anat Embryol Cell Biol 1998; 150: 1–106.
39) Lammens M. Neuronal migration disorder in man. Eur J Morphol 2000; 38: 327–333.
40) Norman MG, McGillivray BC, Kalousel DK, et al. Congenital malformations of the brain. Pathologic, embryologic, clinical, radiologic, and genetic aspects. New York, Oxford University Press. 1995.
41) Berry M, Rogers AW. The migration of neuroblasts in the developing cerebral cortex. J Anat 1965; 99: 691–709.
42) Racik P. Neurons in Rhesus monkey visual cortex: systematic relation between time of origin and eventual disposition. Science 1974; 183: 425–427.
43) Frotscher M. Dual role of Cajal-Retzius cells and reelin in cortical development. Cell Tissue Res 1997; 290: 315–322.
44) Alter M, Liebo J, Desnick SO, et al. The behavior of the reeler neurological mutant mouse. Neurology 1968; 18: 289.
45) Caviness V. Neocortical histogenesis in normal and reeler mice: A developmental study based upon [$^3$H] thymidine autoradiography. Dev Brain Res 1982; 4: 293–302.
46) Soriano E, Alvarado-Mallart RM, Dumesnil N, et al. Cajal-Retzius cells regulate the radial glia phenotype in the adult and developing cerebellum and alter granule cell migration. Neuron 1997; 18: 563–577.
47) Miyata T, Nakajima K, Aruga J, et al. Distribution of a reeler gene-related antigen in the developing cerebellum: An immunohistochemical study with an allogeneic anti-body CR-50 on normal and *reeler* mice. J Comp Neurol 1996; 372: 215–228.
48) Hoffarth RM, Johnston JG, Krushel LA, et al. The mouse mutation *reeler* causes increased adhesion with a subpopulation of early postmitotic cortical neurons. J Neurosci 1995; 15: 4838–4850.
49) Pinto Lord MC, Evrard P, Caviness VS. Obstructed neuronal migration along radial glia fibers in the neocortex of the *reeler* mouse: a Golgi-EM analysis. Dev Brain Res 1982; 4: 379–393.
50) Miller MW. Effect of prenatal exposure to ethanol on the development of cerebral cortex: I. Neuronal generation. Clin Exp Res 1988; 12: 440–449.
51) Miller MW. Migration of cortical neurons is altered by gestational exposure to ethanol. Clin Exp Res 1993; 17: 304–314.
52) Miller MW, Robertson S. Prenatal exposure to ethanol alters the postnatal development and transformation of radial glia to astrocytes in the cortex. J Comp Neurol 1993; 337: 253–266.
53) Sun XZ, Inouye M, Hayasaka S, et al. Effects of different doses of γ-radiation on the developing brain of mice. Environ Med 1995; 39: 113–116.
54) Sun XZ, Inouye M, Fukui Y, et al. An immunohistochemical study of radial glial cells in the mouse brain prenatally exposed to γ-irradiation. J Neuropathol Exp Neurol 1997; 56: 1339–1348.
55) Sun XZ, Inouye M, Takagishi Y, et al. Follow-up study on histogenesis of microcephaly associated with ectopic gray matter induced by prenatal γ–irradiation in the mouse. J Neuropathol Exp Neurol 1996; 55: 357–365.
56) Sun XZ, Takahashi S, Fukui Y, et al. Different patterns of abnormal neuronal migration in the cerebral cortex of mice prenatally exposed to irradiation. Dev Brain Res 1999; 114: 99–108.
57) Sun XZ, Takahashi S, Fukui Y, et al. Neurogenesis of heterotopic gray matter in the brain of the microcephalic mouse. J Neurosci Res 2001; 66: 1083–1093.
58) Shinmura Y, Kosugi I, Aiba-Masago S, et al. Disordered migration and loss of virus-infected neuronal cells in developing mouse brains infected with murine cytomegalocvrus. Acta Neuropathol 1997; 93: 551–557.
59) Sakata-Haga H, Sawada K, Hisano S, et al. Abnormalities of cerebellar foliation in rats prenatally exposed to ethanol. Acta Neuropathol 2001; 102: 36–40.
60) Baraban SC, Wenszel HJ, Hochman DW, et al. Characterization of heterotopic cell clusters in the hippocampus of rats exposed to methylazoxymethanol in utero. Epilepsy Res 2000; 39: 87–102.
61) Colacitti C, Sancini G, DeBiasi S, et al. Prenatal methylazoxymethanol treatment in rats produces brain abnormalities with morphological similarities to human developmental brain dysgeneses. J Neu ropathol Exp Neurol 1999; 58: 92–106.
62) Colacitti C, Sancini G, Franceschetti S. Altered connection between neocortical and heterotopic areas in methylazoxymethanol-treated rat. Epilepsy Res 1998; 32: 49–62.
63) Sun XZ, Fukui Y. Midkine, a new heparin-binding growrh/differentiation factor: expression and distribution during embryogenesis and pathological status. Cong Anom 1998; 38: 25–38.
64) Griffith M. Midkine and secondary neurulation. Teratology 1997; 55: 213–223.
65) Muramatsu H, Inui T, Kimura T, et al. Localization of heparin-binding, neurite outgrowth and antigenic regions in midkine molecule. Biochem Biophys Res Comm 1994; 203: 1131–1139.
66) Muramatsu T. The midkine family of growth differentiation factors. Dev Growth Differ 1994; 36: 1–8.
67) Sun XZ, Takahashi S, Kubota Y, et al. Types and three-dimensional distribution of neuronal ectopias in the brain of mice prenatally subjected to X-irradiation. J Radiat Res 2002; 43: 202–212.
68) Heintz N, Nornan DJ, Gao WQ, et al. Neurogenetic approaches to mammalian brain development. In: Davie ed. Genome Maps and Neurological Disorders. NY: Cold Spring Harbor Press, 1993: 19–44.
69) Hatten ME, Heintz N. Mechanisms of neural patterning and specification in the developing cerebellum. Annu Rev Neurosci 1995; 18: 385–408.
70) Caviness VS. Architectonic map of neocortex of the normal mouse. J Com Neurol 1975; 164–247.
71) Sheppard A, Pearlman A. Abnormal reorganization of preplate neurons and their associated extracellular matrix: an early manifestation of altered neocortical development in the reeler mutant mouse. J Comp Neurol 1997; 378: 173–179.
72) Pesold C, Impagnatiello F, Pisu MG, et al. Reelin is preferentially expressed in neurons synthesizing γ-aminobutyric acid in cortex and hippocampus of adult rats. Proc Natl Acad Sci 1998; 95: 3221–3226.
73) Lambert de Rouvroit C, Goffinet AM. A new view of early cortical development. Biochem Pharmacol 1998; 56: 1403–1409.
74) Senzaki K, Ogawa M, Yagi T. Proteins of the CNR family are multiple receptors for Reelin. Cell 1999; 99: 635–647.
75) Trommsdorff M, Gotthardt M, Hiesberger T, et al. Reeler/Disabled-like disruption of neuronal migration in knockout mice lacking the VLDL receptor and ApoE receptor 2. Cell 1999; 97: 689–701.
76) D'Arcangelo G, Homayouni R, Keshvara L, et al. Reelin is a ligand for lipoprotein receptors. Neuron 1999; 24: 471–479.
77) Hiesberger T, Trommsdorff M, Howell BW, et al. Direct binding of Reelin to VLDL receptor and ApoE receptor 2 induces tyrosine

phosphorylation of disabled-1 and modulates tau phosphorylation. Neuron 1999; 24: 481–489.
78) Dulabon L, Olson EC, Taglienti MG, et al. Reelin binds α3β1-integrin and inhibits neuronal migration. Neuron 2000; 27: 33–44.
79) Howell BW, Gertler FB, Cooper JA. Mouse disabled (mDab1): An Src binding protein implicated in neuronal development. Embo J 1997; 16: 121–132.
80) Thomas SM, Brugge JS. Cellular functions regulated by Scr family kinases. Annu Rev Cell Dev Biol 1997; 13: 513–609.
81) Lowell CA, Soriano P. Knockouts of Src-family kinases: Stiffbones wimpy T cells, and bad memories. Genes Dev 1996; 10: 1845–1857.
82) Brown MT, Cooper JA. Regulation, substrates and functions of scr. Biochim Biophys Acta 1996; 1287: 121–149.
83) Klinghoffer RA, Sachsenmaier C, Cooper JA, et al. Src family kinases are required for integrin but nor PDGFR signal transduction. Embo J 1999; 18: 2459–2471.
84) Zukerberg LR, Patrick GN, Nikolic M, et al. Cables links Cdk5 and c-Ab1 and facilitates Cdk5 tyrosine phosphorylation, kinase upregulation, and neurite outgrowth. Neuron 2000; 26: 633–646.
85) Gilmore EC, Ohshima T, Goffinet AM, et al. Cyclin-dependent kinase 5-deficient mice demonstrate novel developmental arrest in cerebral cortex. J Neurosci 1998; 18: 6370–6377.
86) Chae T, Kwon YT, Bronson R, et al. Mice lacking p35, a neuronal specific activator of Cdk5, display cortical lamination defects, seizures, and adult lethality. Neuron 1997; 18: 29–42.
87) Ohshima T, Ward JM, Huh CG, et al. Targeted disruption of the cyclin-dependent kinase 5 gene results in abnormal corticogenesis, neuronal pathology and perinatal death. Proc Natl Acad Sci U S A 1996; 93: 11173–11178.
88) Nikolic M, Chou MM, Lu W, et al. The p35/Cdk5 kinase is a neuron-specific Rac effector that inhibits Pak1 activity. Nature 1998; 395: 194–198.
89) Manser E, Huang HY, Loo TH, et al. Expression of constitutively active α-PAK reveals effects of the kinase on actin and focal complexes. Mol Cell Biol 1997; 17: 1129–1143.
90) Albrecht U, Abu-Issa R, Ratz B, et al. Patelet-activating factor acetylhydrolase expression and activity suggest a link between neuronal migration and platelet-activating factor. Dev Biol 1996; 180: 579–593.
91) Dobyns WB, Andernann E, Andermann F, et al. X-linked malformations of neuronal migration. Neurology 1996; 47: 331–339.
92) Hattori M, Adachi H, Tsujimoto M, et al. Miller-Dieker lissencephaly gene encodes a subunit of brain platelet-activating factor acetylhydrolase. Nature 1994; 370: 216–218.
93) Ho YS, Swenson L, Derewenda U, et al. Brain acetylhydrolase that inactivates platelet-activating factor is a G-protein-like trimer. Nature 1997; 385: 89–93.
94) Clark GD, Mizguchi M, Antalffy B, et al. Predominant localization of the lis family of gene products to Cajal-Retzius cells and ventricular neuroepithelium in the developing human cortex. J Neuropathol Exp Neurol 1997; 56: 1044–1052.
95) Mizuguchi M, Takashima S, Kakita A, et al. Lissencephaly gene product. Localization in the central nervous system and loss of immunoreactivity in Miller-Dieker syndrome. Am J Pathol 1995; 147: 1142–1151.
96) Dobyns WB, Truwit CL. Lissencephaly and other malformations of cortical development: 1995 an update. Neuroped 1995; 26: 132–147.
97) Ross ME, Srivastava AK, Featherstine T, et al. Linked-age and physical mapping of X-linked lissencephaly/SBH (XLIS): a gene causing neuronal migration defects in human brain. Hum Mol Genet 1997; 6: 555–562.
98) Des Portes V, Pinard JM, Billart P, et al. A novel CNS gene required for neuronal migration and involved in X-linked subcortical laminar heterotopia and lissencephaly syndrome. Cell 1998; 92: 51–61.
99) Gleeson JG, Lin PT, Flanagan LA, et al. Doublecortin is a microtubule-associated protein and is expressed widely by migrating neurons. Neuron 1999; 23: 257–271.
100) Dobyns WB, Truwit CL, Ross ME, et al. Differences in the gyral pattern distinguish chromosome 17-linked and X-linked lissencephaly. Neurology 1999; 53: 270–277.
101) Fink J, Hirsch B, Zheng C, et al. Astrotactin (ASTN), a gene for glal-guided neuronal migration, map to human chromosome lq25.2.Genomics 1997; 40: 202–205.
102) Fink J, Dobyns WB, Guerrini R, et al. Identification of a duplication of Xq28 associates with bilateral periventicular nodular heterotopia. AM J Hum Genet 1997; 61: 379–387.
103) Eksioglu YZ, Scheffer IE, Cardenas P, et al. Periventricular heterotopia – an X-linked dominant epilepsy locus causing aberrant cerebral cortical development. Neuron 1996; 16: 77–87.
104) Fox JW, Lamperti ED, Eksiogly YZ, et al. Mutations in filamin 1 prevent migration of cerebral cortical neurons in human periventricular heterotopia. Neuron 1998; 21: 1315–1325.
105) Moser AB, Rasmussen M, Naidu S, et al. Phenotype of patients with peroxisomal disorders subdivided into sixteen complementation groups. J Pediatr 1995; 127: 13–22.
106) Faust PL, Hatten ME. Targeted deletion of the PEX2 peroxisome assembly gene in mice provides a model for Zellweger syndrome, a human neuronal migration disorder. J Cell Biol 1997; 139: 1293–1305.
107) Baes M, Gressens P, Baumgart E, et al. A mouse model for Zellweger syndrome. Nat Genet 1997; 17: 49–57.
108) D'Arcangelo G, Curran T. Reeler: new tales on an old mutant mouse. Bio Essays 1998; 20: 235–244.
109) Hirotsune S, Pack SD, Chong SS, et al. Genomic organization of the murine Miller-Dieker/lissencephaly region: conservation of linkage with the human region. Genome Res 1997; 7: 625–634.
110) Gonzalez JL, Ruso CJ, Goldowitz D, et al. Birthdate and cell marker analysis of scrambler: a novel mutation affecting cortical development with a reeler-like phenotype. J Neurosci 1997; 17: 9204–9211.
111) Ware ML, Fox JW, Gonzalez JL, et al. Aberrant splicing of a mouse disabled homolog mdab1 in the scrambler mouse. Neuron 1997; 19: 239–249.
112) Yoneshima H, Nagata E, Matsumoto M, et al. A novel neurological mutation mouse, yotari, which exhibits reeler-like phenotype but expresses CR-50 antigen/reelin. Neuronsci Res 1997; 29: 217–223.
113) Sheldon M, Rice D, D'Arcangelo G, et al. Scrambler and yotari disrupt the disabled gene and produce a reeler-like phenotype in mice. Nature 1997; 389: 730–733.
114) Hoshino K, Kameyama Y. Developmental-stage-dependent radiosensitivity of neural cells in the ventricular zone of telencephalon in mouse and rat fetuses. Teratology 1988; 37: 257–262.
115) Gressens P, Kosofsky BE, Evrard P. Cocaine-induced disturbances of corticogenesis in the developing murine brain. Neurosci Lett 1992; 140: 113–116.
116) Lee KS, Schottler F, Collins JL, et al. A genetic animal model of human neocortical heterotopia associated with seizures. J Neurosci 1997; 17: 6236–6242.
117) McKusick VA. Mendelian inheritance in man. Catalogs of human genes and genetic disorders. Baltimore, MD: Johns Hopkins Univ Press, 11th ed, 1994.
118) Pilz DT, Matsumoto N, Minnerath S, et al. LISI and XLIS (doublecortin) mutations cause most human classical lissencephaly, but different patterns of malformation. Hum Mol Genet 1998; 7: 2029–2037.
119) Dobyns WB, Guerrini R, Czapansky-Beilman DK, et al. Bilateral periventricular nodular heterotopia with mental retardation and syndactyly in boys: a new X-linked mental retardation syndrome. Neurolgoy 1997; 49: 1042–1047.

Received April 1, 2002; accepted June 21, 2002