

Reelin' in Genes for Cortical Dysplasia

Peter B. Crino, M.D., Ph.D.

Department of Neurology and PENN Epilepsy Center,
University of Pennsylvania School of Medicine,
Philadelphia, Pennsylvania

Malformations of cortical development are a broad family of disorders that are characterized by abnormal cytoarchitecture of the cerebral cortex and a high association with epilepsy. In recent years positional cloning strategies have been implemented to identify several distinct gene mutations that are responsible for developmental brain malformations. The defined functional roles of proteins encoded by these genes have provided pivotal insights into the cellular mechanisms of brain development. Identification of these genes provides important clinical information used in genetic counseling for patients and their families.

A recent study by Hong et al. (1) demonstrated two family pedigrees in which autosomal recessive lissencephaly associated with cerebellar and brainstem hypoplasia was found to be associated with mutations in the human gene encoding reelin. The report was interesting from two perspectives. First, since there is a subpopulation of patients with lissencephaly in whom mutations in the two known lissencephaly genes, *LIS-1* and *doublecortin (DCX)* cannot be identified, mutations in the *reelin* gene provide a new screening tool to define the molecular genetics of lissencephaly in an even broader patient population. Second, and perhaps more compelling, the study by Hong et al. demonstrates clearly how mouse mutant strains have aided in defining human malformations of cortical development (MCD) genes since these authors predicated their mutational screen on pathological similarities between the probands and the reeler mouse strain. The reeler mouse which exhibits an MCD characterized by an inversion of cerebral cortical layers as well as cerebellar and brainstem abnormalities, has been

studied for over 25 years and the gene responsible for this MCD, *reelin*, was identified 6 years ago (2).

MCD include a heterogeneous group of disorders (cortical dysplasias, CD) in which the hexalaminar structure of the cerebral cortex is disrupted and individual neural cytoarchitecture may be aberrant (for review see reference 3). MCD can uniformly affect broad regions of the cerebral cortex, as in classical lissencephaly or hemimegalencephaly, or may be restricted to focal areas such as tubers in the tuberous sclerosis complex (TSC) or Taylor-type focal cortical dysplasia (FCD). Additionally, the morphology of single neurons in MCD is often abnormal, suggesting a more pervasive disruption of cerebral cortical development. Many MCDs have been recognized prior to the turn of the twentieth century, when they were categorized on the basis of structural pathological features, i.e., agyria and pachygyria. However, the recent advances in high resolution magnetic resonance imaging (MRI) coupled with identified gene mutations in select MCD suggests that more precise terminologies will be available in the future.

Clinical Problems in Patients with MCD

The spectrum of neuropsychiatric deficits associated with MCD often reflects the anatomic extent of the cortical malformation. For example, profound mental retardation is common in patients with MCD such as lissencephaly affecting broad cortical regions. In patients with multifocal lesions such as TSC, mild to severe cognitive deficits and autism may be present. In those individuals with MCD affecting restricted cortical regions or subcortical regions, only subtle cognitive changes or even normal cognitive function is observed. The single unifying feature of virtually all MCD, however, is a high association with epilepsy. For example, it is estimated that MCD may account for 20% of epilepsy patients (4,5) and in select disorders such as lissencephaly, hemimegalencephaly, and TSC, seizures are present in over 70–90% of patients. Recent evidence suggests that even smaller regions of CD may play a pivotal role in epileptogenesis, since nearly 30% of focal cortical resections aimed at treating neocortical epilepsy contain some type of CD. With the recent advances in neuroimaging, many cases of “cryptogenic” epilepsy are now found to result from small regions of cortex with subtle albeit abnormal cytoarchitecture (microdysgenesis). Finally, an ever increasing number of patients with temporal lobe epilepsy exhibit radiographic and histopathologic evidence of CD either alone or in combination with hippocampal sclerosis (“dual pathology” patients).

Address correspondence to: Peter B. Crino, M.D., Dept. of Neurology, University of Pennsylvania, 3 West Gates Bldg., 3400 Spruce St., Philadelphia, PA 19104; E-mail: crinop@mail.med.upenn.edu

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There are several explanations for the high association of MCD with epilepsy. The most likely cause is disruption of synaptic connectivity that accompanies most MCD. This has been suggested by intracranial EEG (6,7) as well as in vitro slice recording from human specimens (8,9). Additionally, the molecular pharmacologic profile of individual neurons in MCD may be distinct from the normal state and the expression of important genes such as neurotransmitter receptors, synthetic enzymes, and uptake sites may be altered (10,11,12). These changes likely result in the development of hyperexcitability (13). Virtually all seizure subtypes—generalized tonic-clonic, complex partial, atonic, myoclonic, and atypical absence seizures as well as infantile spasms—have been described when the broad family of MCD are considered *in toto*.

Satisfactory seizure control in patients with MCD may be particularly difficult to attain despite antiepileptic drug (AED) polytherapy and surgical resection is often necessary. Unfortunately, even with heroic attempts at localization of the seizure focus and skilled neurosurgical technique, seizure cure following surgical resection of focal CDs is achieved in less than 50% of patients; even worse, a subpopulation of individuals are not surgical candidates at all. Thus, it is my view that patients with MCD provide a new and unique challenge in epilepsy therapy in this century since too many individuals do not benefit from current medical or surgical approaches.

Disorganization and Development, Malformations and Molecules

Only in the past decade have we begun to understand the molecular pathogenesis of select MCD. Positional cloning strategies in human patients with inherited forms of MCD have led to the identification of at least eight genes directly responsible for human MCD that are associated with epilepsy, and most of these genes are being studied in engineered mouse strains. Furthermore, as the field of developmental neurobiology progresses at a dizzying pace, animal strains have been engineered using transgenic technologies that model human MCD so that the cell pathways leading to aberrant cortical lamination can be studied in detail (see review by reference 14). Indeed, the report by Hong et al. (1) demonstrates how similarities between mouse and human phenotypes may be directly implemented to screen for candidate MCD genes in patients. These important results have clearly shown that the molecular pathogenesis of MCD can now be addressed in experimental model systems rather than by structural classification and that single gene mutations can be identified even in rare disorders or when the inheritance pattern may be unclear. MCD may be observed in the setting of large chromosomal rearrangements such as trisomy syndromes and in a variety of additional neurological disorders without a definitive molecular

correlate such as dyslexia, autism, and schizophrenia. This review will provide an overview focusing on identified genes that have been linked to MCD (for more in depth review, see reference 15).

A central issue in understanding the pathogenesis of each MCD syndrome is defining the molecular events that cause the malformation and then, putting these events in the appropriate developmental context. Development of the cerebral cortex is initiated at gestational week 7 and continues through week 24 (for review, see references 16,17). The cortex is formed in three broad stages: (1) mitosis and proliferation of neural progenitor cells in the ventricular zone (VZ), (2) dynamic migration of postmitotic neurons out of the VZ and (3) the establishment of cortical laminae in the evolving cortical plate through an “inside-out gradient.” Neurons destined to reside in deeper cortical laminae, e.g., layer VI, arrive in the nascent cortical plate first, and subsequent waves of neurons destined for more superficial layers migrate through each preceding and established layer. Presumably, the gene mutations cause MCD at critical points during one of these three epochs, and these time-points provide a framework to understand the interface between gene mutations and neural development. Thus, a gene mutation that alters cytoskeletal assembly during neuronal migration will have distinct effects in an actively migrating neuron versus a neuron that has already achieved its laminar destination.

Disorders of Cellular Proliferation

Tubers are regions of focal CD identified in TSC that are highly associated with epilepsy and are the likely source of seizure initiation in TSC patients (18,19). Microscopically, the normal hexalaminar structure of cortex is lost within the tuber. Dysplastic neurons and giant cells, a unique cell type not seen in any other neurologic disorder, are found in tubers as well as extensive astrocytosis (for review, see reference 20). Tubers are believed to result from an early defect in neural precursor cell proliferation in which failed maturation of individual neurons gives rise to the characteristic cell types. Dysplastic cells in tubers likely exhibit deficits in neural migration as well, since there is a loss of normal lamination.

After nearly a decade of investigation, the European Tuberos Sclerosis Consortium identified and cloned the *TSC2* gene in 1993, which encodes the 200kD protein tuberin. Subsequently, the *TSC1* gene was identified. That gene encodes a protein, hamartin, that is structurally distinct from tuberin and has virtually no homology to known vertebrate genes (21). Both hamartin and tuberin mRNA and protein are widely expressed in normal tissues including brain, liver, adrenal cortex, cardiac muscle, skin, and kidney.

Identification of an encoded coiled-coil domain in the carboxy region of hamartin raised the possibility of a functional protein-protein interaction with tuberin (and other pro-

teins). Indeed, hamartin interacts with the ezrin-radixin-moesin (ERM) family of actin-binding proteins and may contribute to cell-cell interactions, cell adhesion, and cell migration (22). Loss of hamartin function following *TSC1* mutations may lead to early defects in cell proliferation but may also compromise neuronal migration. Tuberin contains a hydrophobic N-terminal domain and a conserved 163 amino acid carboxy terminal region that exhibits sequence homology to the catalytic domain of a GTPase activating protein (GAP) for Rap1. As a member of the superfamily of Ras-related protein, Rap1 likely functions in regulation of DNA synthesis and cell cycle transition. Tuberin displays GAP activity for Rap1, but not Rap2, Ha-Ras, Rac, or Rho and co-localizes with Rap1 in the Golgi apparatus in several cell lines (23). The GAP activity of functional tuberin may modulate the effects of Rap1 on G- to S-phase transition during cell division. Mutations in *TSC2* might result in constitutive activation of Rap1 leading to enhanced cell proliferation or incomplete cellular differentiation.

Disorders of Neuronal Migration

One of the earliest MCD genes discovered was *LIS-1* (later named *PFAFH1B1* when it was identified as a subunit of platelet activating factor acetyl hydrolase) on chromosome 17p13.3 in patients with the autosomal recessive Miller-Dieker lissencephaly syndrome (24). The Miller-Dieker lissencephaly syndrome is an autosomal disorder characterized by classical lissencephaly, profound mental retardation, epilepsy, and craniofacial dysmorphism. In classical lissencephaly, the cerebral cortex is thickened and without gyri. The cerebral cortex is characterized by only four layers, including a marginal, superficial cellular, sparsely cellular, and deep cellular laminae. Cells in the deeper layers are dysmorphic and exhibit features of either pyramidal, fusiform, or rounded neurons without clear radial orientation. The encoded *LIS-1* protein, PFAFH1B, contains repetitive stereotyped tryptophan and aspartate repeats (WD40 repeats) and functions as a degradative enzyme for platelet activating factor that may modulate neuronal calcium flux, and may bind to select tyrosine kinase receptors. Recent evidence suggests that mutations in the *PFAFH1B1* gene may lead to defective nucleokinesis (movement of the neuronal nucleus during dynamic phases of neural migration). The LIS1 protein interacts with microtubules, and two identified LIS-interacting proteins, Nudel and mammalian homolog NudE, are components of the dynein motor complex and microtubule organizing centers (25). In mutant *LIS-1* mouse strains, there is a range of disorganization of cortical cytoarchitecture including abnormal hippocampal and cortical lamination (26) and electrophysiologic studies have demonstrated hyperexcitability (27).

X-linked lissencephaly (XLIS) is also a classical lissencephaly although a few abnormally large gyri (pachygyri) may be noted. While the neuropathologic features of XLIS are vir-

tually indistinguishable from Miller-Dieker, lissencephaly and mental retardation and epilepsy are invariably present. There are no associated craniofacial abnormalities in XLIS. Mutations in the doublecortin gene (*DCX*) on chromosome Xq22 in hemizygous males results in lissencephaly (28,29) whereas in females *DCX* gene mutations result in the subcortical band heterotopia syndrome (see below). *DCX* protein is normally expressed during the limited time window surrounding neuronal migration, and thus mutational effects will be exerted only during this phase of cortical development. *DCX* interacts with microtubules of the neuronal cytoskeleton and co-precipitates with LIS-1 protein (30), suggesting that these two molecules may reflect a pivotal pathway in assembly of the neuronal cytoskeleton during dynamic phases of neuronal migration. A related molecule, Doublecortin-like kinase (DCLK) shares sequence similarity to *DCX* in its N-terminal region and is also co-localized with microtubules (24). *DCX* contains a consensus substrate site for c-Abl, a non-receptor tyrosine kinase that also modulates cytoskeletal assembly (28). The association with c-Abl may herald an important mechanistic link to specific cell pathways since a mutation in the mouse *disabled1* gene, a c-Abl binding protein, also results in abnormal neuronal migration.

Periventricular nodular heterotopia (PH) and subcortical band heterotopia (SBH) are X-linked disorders characterized by differential phenotypes in males and females (for review see reference 31). Nodules of abnormal neurons and astrocytes separated by layers of myelinated fibers are identified along the lateral ventricles beneath the cortex in female PH patients (16,32). An important recent study using human depth electrode recording showed that seizures in patients with PH may emanate directly from the heterotopia (33). PH results from mutations in the *filamin1* (*FLN1*) gene which is located on chromosome Xq28 (34). The encoded protein filamin1 is an actin-cross-linking phosphoprotein that modulates actin reorganization necessary for cellular locomotion. The precise mechanisms by which loss of filamin1 function in PH leads to nodular accumulations of neurons remains to be fully defined. While *DCX* gene mutations in males cause XLIS, *DCX* gene mutations in females are associated with the subcortical band heterotopia ("double cortex") syndrome in which there is a bilaterally symmetric band of cortical neurons extending through the underlying white matter of the centrum semiovale (for review and radiographic features see reference 35). The subcortical bands contains heterotopic neurons which are of small pyramidal shape without clear radial orientation. Neurons may be arrayed into clusters, sheets, or wide bands. Of interest, the overlying cortex exhibits normal cytoarchitecture. The subcortical band heterotopia is separated from the overlying cortex and underlying ventricles by normal white matter. Of interest, in a rat model for subcortical band heterotopia, seizures were shown to emanate the overlying cortex (36) although this finding has not been demonstrated in humans.

The fascinating sexual dimorphism of the PH and SBH/ XLIS syndromes likely reflects differential expression of the mutant or normal *filamin 1* or *DCX* gene alleles on the X-chromosomes. Females with PH or SBH, carry one normal allele and one mutant allele for either the *filamin 1* or *DCX* genes. As a consequence of X-chromosome inactivation (Lyonization), one of these alleles is no longer used for gene transcription. It has been speculated that neurons in which the normal allele is inactivated and the mutant gene is expressed, will become the cellular constituents of either the nodules in PH or the band heterotopia in subcortical band heterotopia. Conversely, those cells expressing the normal allele will comprise the overlying and putatively “normal” cortex. This attractive hypothesis awaits formal proof.

Disorders of Unspecified Developmental Etiology

Two additional and rare disorders are the Fukuyama muscular dystrophy syndrome (FCMD) and muscle-eye-brain disease (MEB). These autosomal recessive disorders exhibit “cobblestone” lissencephaly in which there is a complete loss of regional and laminar organization that is distinct from classical lissencephalies such as the Miller-Diecker syndrome. FCMD syndrome is seen primarily in Japan and is associated with a debilitating muscular dystrophy as well as seizures. The FCMD syndrome gene encodes the protein fukutin, which maps chromosome 9q31 (37) and may function as a secreted protein. Muscle-eye-brain disease is associated with retinal dysplasia, congenital myopathy, and lissencephaly. The muscle-eye-brain disease gene, though not yet cloned, is located on chromosome 1p32-p34 (38).

The search for candidate genes responsible for Taylor type of FCD is an area of intense research. While this dysplasia subtype rarely, if ever, has a familial inheritance pattern, the histologic features of FCD suggest a consistent or uniform etiology (39). It has been speculated that FCD results from early somatic mutations in one of the known MCD genes, or in a yet to be defined, or even novel gene. Alternatively, speculations suggest that FCD is a late occurring event possibly even a post-natal event (40) resulting from external injury such as trauma or hypoxia-ischemia. An interesting recent study demonstrates discordant incidence of select FCD in monozygotic twins suggesting that these lesions result from acquired factors, such as prenatal insults and postfertilization genetic abnormalities (41). Furthermore, it is not clear at what point in cortical development FCD occurs and whether it reflects an abnormality in cell proliferation, migration, or laminar destination.

Summary and New Directions: Targeted Therapy for Epilepsy in MCD

Prior to the 1990's, the molecular pathogenesis of MCD was largely the source of speculation. However, with the discovery of several genes responsible for MCD including *LIS1*, *dou-*

blecortin, *FLN1*, *TSC1*, and *TSC2*, it is clear that single gene mutations may account for numerous subtypes of MCD. The identification of MCD genes now permits in depth analysis of the proteins encoded by these genes and may aid in designing new therapies targeted at these molecules. Thus, in the future, we may hope to modulate pathways in select MCD syndromes so that specific agents can be used to treat seizures in, for example, PH or TSC. Perhaps even more exciting is the potential to design therapeutic strategies to actually abolish or prevent the formation of these malformations *in utero*.

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