Malformations of the Cerebral Cortex as a Cause of Mental Retardation and Epilepsy: Anatomoclinical and Genetic Spectrum*

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Summary

The malformations of the cerebral cortex represent a major cause of developmental disabilities, severe epilepsy and reproductive disadvantage. The advent of high resolution MRI techniques has facilitated the in vivo identification of a large group of cortical malformation phenotypes. Several malformation syndromes caused by abnormal cortical development have been recognized and specific causative gene defects have been identified.

Periventricular nodular heterotopia is a malformation of neuronal migration in which a subset of neurons fails to migrate into the developing cerebral cortex. X-linked Periventricular Nodular Heterotopia (PNH) is mainly seen in females and is often associated with focal epilepsy. FLNA mutations have been reported in all familial cases and in about 25% of sporadic patients. A rare recessive form of PNH due ARGEF2 gene mutations has also been reported in children with microcephaly, severe delay and early seizures.

Lissencephaly-pachygyria and subcortical band heterotopia are disorders of neuronal migration and represent a malformative spectrum resulting from mutations of either LIS1 or DCX genes. LIS1 mutations cause a more severe malformation in the posterior brain regions. Most children have severe developmental delay and infantile spasms, but milder phenotypes are on record, including posterior subcortical band heterotopia owing to mosaic mutations of LIS1. DCX mutations usually cause anteriorly predominant lissencephaly in males and subcortical band heterotopia in female patients. Mutations of DCX have also been found in male patients with anterior subcortical band heterotopia and in female relatives with normal brain magnetic resonance imaging.

Autosomal recessive lissencephaly with cerebellar hypoplasia, accompanied by severe delay, hypotonia, and seizures, has been associated with mutations of the reelin (RELN) gene. X-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia in genotypic males is associated with mutations of the ARX gene. Affected boys have severe delay and seizures with suppression-burst EEG. Early death is frequent. Carrier female patients can have isolated corpus callosum agenesis.

Among several syndromes featuring polymicrogyria, bilateral perisylvian polymicrogyria shows genetic heterogeneity, including linkage to chromosome Xq28 in some pedigrees, autosomal dominant or recessive inheritance in others, and an association with chromosome 22q11.2 deletion in some patients. About 65% of patients have severe epilepsy. Recessive bilateral frontoparietal polymicrogyria has been associated with mutations of the GPR56 gene.

Epilepsy is often present in patients with cortical malformations and tends to be severe, although its incidence and type vary in different malformations. It is estimated that up to 40% of children with drug-resistant epilepsy have a cortical malformation. However, the physiopathological mechanisms relating cortical malformations to epilepsy remain elusive.

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Keywords: cortical malformations, periventricular nodular heterotopia, lissencephaly, polymicrogyria, genetics, epilepsy

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Missbildungen des zerebralen Kortex als Ursache von mentaler Retardation und Epilepsie: Anatomoklinisches und genetisches Spektrum

Missbildungen der Hirnrinde gehören zu den Hauptursachen von Entwicklungsstörungen, schwerer Epilepsie und Reproduktionsproblemen. Die Entwicklung der hoch auflösenden MRI-Technologie hat die *in vivo* Identifikation einer grossen Anzahl von Hirnrindemissbildungsphänotypen erleichtert. Mehrere auf eine abnorme Entwicklung der Hirnrinde zurückzuführende Missbildungssyndrome wurden erkannt und die spezifisch damit zusammenhängenden genetischen Defekte sind identifiziert worden.

Die periventrikuläre nodulare Heterotopie ist eine Fehlentwicklung der neuronalen Migration, wobei eine Untergruppe von Neuronen nicht in die sich entwickelnde Hirnrinde wandert. Die X-gebundene periventrikuläre nodulare Heterotopie (PNH) ist fast ausschliesslich bei Frauen anzutreffen, häufig in Verbindung mit einer fokalen Epilepsie. FLNA-Mutationen wurden bei allen hereditären Fällen beobachtet und in ungefähr 25% der Patienten mit sporadischen Anfällen. Eine seltene, rezessive, von Mutationen des ARGEF2-Gens verursachte Form von PNH wurde auch bei Kin-

dern mit Mikrozephalie, gravierender Retardierung und Anfällen im frühsten Kindesalter festgestellt.

Lissenzephalie-Pachygyrie und subkortikale Bandheterotopie sind Störungen in der neuronalen Wanderung und drücken sich aus in einem breiten Spektrum von Fehlbildungen der hinteren Hirnregionen. Die meisten davon betroffenen Kinder fallen auf durch ein schweres Entwicklungsdefizit und infantile Spasmen, leichtere Phänotypen sind jedoch bekannt, inklusive einer posterior subkortikalen Bandheterotopie aufgrund von mosaizistischen Mutationen des LIS1-Gens. DCX-Mutationen verursachen normalerweise hauptsächlich im anterioren Bereich vorkommende Lissenzephalien bei männlichen Patienten und subkortikale Bandheterotopien bei weiblichen Patienten. DCX-Mutationen wurden auch bei männlichen Patienten mit anteriorer subkortikaler Bandheterotopie und bei ihren weiblichen Verwandten mit einer normalen MRI-Hirnbildgebung gefunden.

Eine autosomale rezessive Lissenzephalie mit Kleinhirnhypoplasie, verbunden mit gravierender Retardierung, Hypotonie und Anfällen wurde abgeleitet aus Mutationen des Reelin kodierenden RELN-Gens. X-verbundene Lissenzephalie mit Agenesie des Corpus callosum und unterentwickelten Genitalien findet man bei genotypischen männlichen Patienten mit Mutationen des ARX-Gens. Betroffene Knaben weisen eine gravierende Retardierung auf und Anfälle mit einem „Suppression-Burst-EEG". Häufig tritt der Tod sehr früh ein. Trägerpatientinnen können vereinzelt eine Corpus-callosum-Agenesie aufweisen.

Unter den verschiedenen Polymikrogyriesyndromen zeigt die bilaterale perisylvische Polymikrogyrie genetisch ein heterogenes Bild mit Verbindung zum Xq28-Chromosom bei einigen Stammbäumen und Deletion des 22q11.2-Chromosoms bei anderen. Etwa 65% der Patienten leiden an einer schweren Epilepsie. Rezessive bilaterale frontoparietale Polymikrogyrie ist in Verbindung gebracht worden mit Mutationen des GPR56-Gens.

Epilepsie ist oft in tendenziell gravierender Form vorhanden bei Patienten mit kortikalen Fehlbildungen, obwohl Auftretenshäufigkeit und -art je nach Fehlbildung variieren können. Schätzungsweise etwa 40% der Kinder mit einer therapieresistenten Epilepsie leiden unter einer kortikalen Fehlbildung. Die physiopathologischen Mechanismen, welche eine Verbindung von kortikalen Fehlbildungen und Epilepsie erklären könnten bleiben uns jedoch momentan noch verschlossen.

Schlüsselwörter: kortikale Fehlbildungen, periventrikuläre nodulare Heterotopie, Lissenzephalie, Polymikrogyrie, Genetik, Epilepsie

Les malformations du cortex cérébral comme origine de retardements mentaux et d'épilepsie : spectre anatomoclinique et génétique

Les malformations du cortex cérébral représentent une cause majeure de troubles du développement, d'épilepsies graves et de problèmes de la procréation. La mise au point des techniques IRM à haute résolution a facilité l'identification in vivo d'un vaste groupe de phénotypes de malformations corticales. Plusieurs syndromes liés à des malformations imputables à un développement cortical anormal ont été reconnus et la causalité de certains défauts de gènes spécifiques a été identifiée.

L'hétérotopie nodulaire périventriculaire est une malformation de la migration neuronale où un sous-groupe de neurones ne migre pas dans le cortex en voie de développement. L'hétérotopie nodulaire périventriculaire (PNH) liée à l'X apparaît surtout chez les sujets féminins et elle est souvent associée à une épilepsie focale. Des mutations du gène FLNA ont été rapportées dans tous les cas familiaux et dans à peu près 25% des patients à épilepsies sporadiques. Une forme rare de PNH due à des mutations du gène ARGEF2 a également été rapportée chez les enfants avec une microcéphalie, un retardement mental sévère et des attaques précoces.

La lissencéphalie de type pachygyrie et l'hétérotopie sous-corticale en bandes sont des troubles de la migration neuronale et présentent un spectre de malformations résultant de mutations soit du gène LIS1 ou du gène DCX. Les mutations du gène LIS1 provoquent des malformations plus sévères dans les régions postérieures du cerveau. La plupart des enfants sont gravement retardés dans leur développement et souffrent de spasmes infantiles, mais des phénotypes moins sévères ont été rapportés, y compris des cas d'hétérotopie sous-corticale en bandes dues à des mutations en mosaïque du gène LIS1. Les mutations de DCX provoquent généralement une lissencéphalie antérieure prédominante chez les sujets masculins et une hétérotopie sous-corticale en bandes chez les patientes féminines. Des mutations du gène DCX ont également été détectées dans les patients masculins avec une hétérotopie sous-corticale antérieure et leurs parentes avec un diagnostic IRM normal du cerveau.

La lissencéphalie à hypoplasie cérébellaire accompagnée de retards graves du développement mental, d'hypotonie et de crises a été associée aux mutations du codant de la reeline, le gène RELN. La lissencéphalie liée à l'X avec agénésie du corps calleux et organes génitaux ambigus dans les sujets masculins génotypiques est associée aux mutations du gène ARX. Les garçons affectés souffrent de retards mentaux graves et de crises avec un tracé EEG de type suppression-burst. Une mort précoce est fréquente. Des agénésies isolées du corps calleux ont été rapportés chez les patientes porteuses.

Parmi les syndromes à polymicrogyrie, la polymicrogyrie périsylvienne bilatérale se distingue par son hétérogénéité génétique, affichant un lien avec le chromosome Xq28 dans certaines lignées, un héritage autosomique dominant ou récessif dans d'autres, le tout en association avec une délétion du chromosome 22q11.2 chez certains patients. A peu près 65% des patients souffrent d'une épilepsie grave. La polymicrogyrie bilatérale frontopariétale a été citée en rapport avec les mutations du gène GPR56.

L'épilepsie s'observe fréquemment chez les patients avec une malformation corticale, souvent sous une forme grave, bien que l'incidence et le type varient selon les malformations. On estime qu'environ 40% des enfants avec une épilepsie pharmacoréfractaire présentent une malformation corticale. Cependant, les mécanismes liant les malformations corticales à l'épilepsie nous échappent encore.

Mots clés : malformations corticales, hétérotopie nodulaire périventriculaire, lissencéphalie, polymicrogyrie, génétique, épilepsie

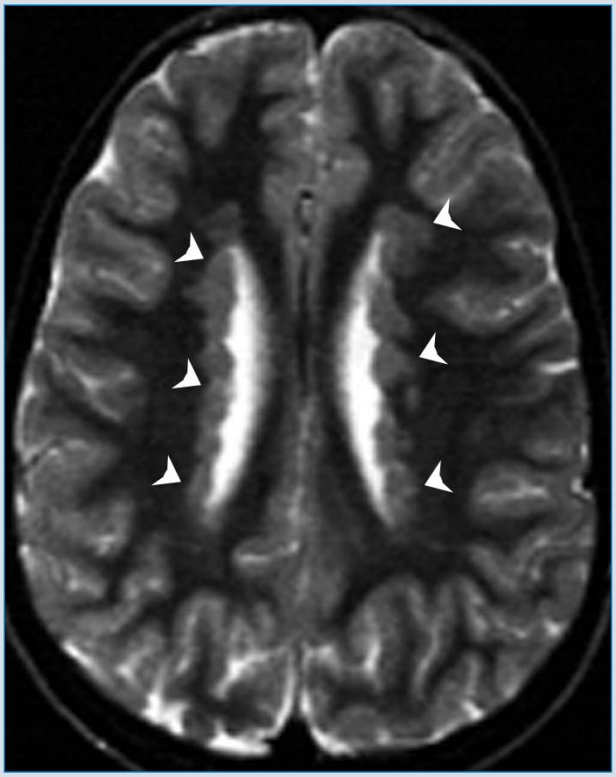

Figure 1: Brain MRI scan; axial section. Typical classic bilateral periventricular nodular heterotopia in a woman with a missense mutation of the FLNA gene. Bilateral nodules of subependymal heterotopia are contiguous and rather symmetric, extensively lining the ventricular walls (white arrows). Patients with periventricular heterotopia different from that reproduced in this picture have very low chances of carrying a mutation on the FLNA gene.

Introduction

The genetic malformations of the cerebral cortex are usually characterized by malposition and abnormal differentiation of grey matter [1]. The development of human cerebral cortex can be divided into three overlapping stages. During the first stage, stem cells proliferate and differentiate into young neurons or glial cells deep in the forebrain, in the ventricular and subventricular zones lining the cerebral cavity. In the second phase, after their final mitotic division, cortical neurons migrate away from their place of origin in a radial fashion – along the radial glial fibres from the periventricular region, or tangentially, primarily from the ganglionic eminences – towards the pial surface, where each successive generation passes one another and settles in an inside-out pattern within the cortical plate. The third phase represents cortical organization within six layers associated with synaptogenesis and apoptosis. This is a dynamic process and more than one stage may occur simultaneously during several gestational weeks. In humans, the proliferation stage ranges from weeks 5-6 to weeks 16-20, migration from weeks 6-7 to weeks 20-24, and organization from week 16 until well into postnatal life.

When migration is complete, the cortex is a six-layered structure, with each layer comprising different types of neurons that form discrete connections within the CNS and perform distinct functions. The abnormalities that primarily affect proliferation are usually associated with an alteration in both neuronal and glial cell differentiation, producing abnormal cell size and morphology [2]. Disorders affecting neuronal migration are characterized by abnormal neuronal positioning [2]. When migration is arrested during later cortical development, abnormal cell position is more likely to be restricted to the cortex.

Genetic studies of cerebral cortex development and neuronal migration have been remarkably successful over the past few years, uncovering several genes that, when mutated, cause disorders of neuronal migration and cerebral cortical development in mice and in humans [1]. Epilepsy is often present in patients with malformations of cortical development and tends to be severe, although its incidence and type vary in different malformations [3]. It is estimated that up to 40% of children with drug-resistant epilepsy have a cortical malformation [4].

In the following sections we will discuss the most frequent cortical malformations causing epilepsy and those for which the causative gene has been cloned (**Table 1**).

Table 1:
Most frequent cortical malformations causing epilepsy and their, currently known, causative genes

Cortical malformation	Inheritance	Locus	gene	Gene product/function
Bilateral periventricular nodular heterotopia	X-linked AR	Xq28 20q13.13	FLNA ARFGEF2	FLNA: actin-binding protein; coagulation and vascular-related functions
Isolated lissencephaly	AD X-linked	17p13.3 Xq22.3	LIS1 or PAFAH1B1 DCX	LIS1: platelet-activation factor acetylhydrolas E, isoform 1B, a subunit; regulates the level of platelet activating factor in the brain; interaction with dynein, dynactin, NUDE, and NUDEL proteins
Double cortex (subcortical band heterotopia)	X-linked AD	Xq22.3 17p13.3	DCX LIS1 or PAFAH1B1	Doublecortin; interaction with LIS1; ?effect on microtubules and cytoskeleton
Miller-Dieker	Microdeletion disorder	17p13.3	LIS1, 14-3-3-epsilon and contiguous genes	
Lissencephaly with cerebellar hypoplasia	AR	7q22	RELN VLDLR	Reelin; control cell-cell interactions critical for cell positioning in the brain Very low density lipoprotein receptor; reelin signalling pathway
Lissencephaly with abnormal genitalia	X-linked	Xp22.13	ARX	Aristaless-related homeobox gene; tangential migration & differentiation of GABAergic interneurons in the ganglionic eminence and neocortex
Polymicrogyria				
Bilateral perisylvian	X-linked	Xq28	?	
(1 sibship)	AD	11p13	PAX6	Transcription factor
(1 sibship)	Mitochondrial		MTTL1	
Bilateral fronto-parietal	AR		GPR56	G Protein coupled receptor; role in regional patterning of the cerebral cortex
Schizencephaly	AD?	10q26.1	EMX2 (not confirmed)	Homeobox gene; transcription factor acting as a regulatory gene

Malformations due to abnormal neuronal migration

Periventricular Nodular Heterotopia (PNH)

PNH, often bilateral, consists of confluent nodules of grey matter located along the lateral ventricles due to a total failure of migration of some neurons (**Figure 1**). Although most patients with PNH come to medical attention because they have epileptic seizures without additional neurological abnormalities, there is a wide spectrum of clinical presentations with some correlation between the size of PNH and the likelihood of concomitant cortical impairment and clinical severity [5, 6].

PNH is an X-linked dominant disorder (MIM #300049) that displays high rates of embryonic hemizygous male lethality [7-9]. PNH is therefore generally regarded as a cell-autonomous mosaic phenotype, in females, due to random X-inactivation, where neurons that express the mutant X chromosome fail to migrate and neurons that express the normal X chromosome migrate properly. Almost 100% of families with X-linked bilateral PNH and about 20% of sporadic patients harbour mutations of the filamin 1 gene [FLNA] [10, 8, 9]. The low percentage of FLNA mutations in sporadic cases could be explained by low somatic mosaicism [11, 12], as well as the viability of some affected males.

FLNA maps to Xq28, is composed of 48 exons, spans a 26 kb genomic region and codes for the F-actin-binding cytoplasmic cross-linking phosphoprotein Filamin A (FLNA) [13, 14], composed by three major functional domains: 1) a tandem N-terminal calponin-homology domain (CHD1 and CHD2), conferring F-actin binding

properties; 2) 15 + 8 internally homologous Ig-like repeats separated by a short run with an unique sequence (hinge‰ 1), important for flexibility; 3) a second short run (hinge% 2) followed by the C-terminal repeat 24, that are important for binding to a wide range of proteins and for dimerization [15-17]. The N-terminal actin-binding domain displays strong structural and functional similarity to the N-terminal domains of dystrophin, alpha-actin and beta-spectrin. The 24th repeat is truncated, allowing dimerization of two FLNA molecules at the C terminus [17]. FLNA dimers bind membrane-associated proteins such as b1 and b2 integrins [18, 19]; tissue factor [20], and presenilin1 [21]. FLNA can also bind other membrane-associated molecules, such as glycoprotein Iba, through repeats further from the C terminus [22]. A model of FLNA function postulates that, in FLNA-deficient neurons, part of the essential migratory motor is defective and that these defective neurons are incapable of migration. An alternative model proposes that FLNA acts earlier in development, as a component of a switch that is required for a neuron to become competent for subsequent migration. In the latter model, FLNA still functions by structuring actin networks at the cell periphery, but instead of acting at the leading edge of the migrating neuron, FLNA maintains a static focal contact between a stationary neuron and a neighbouring radial glial cell. FLNA also promotes orthogonal branching of actin filaments [17] and is important for coagulation and vascular development. These coagulation and vascular-related functions of FLNA might account for the prenatal male lethality observed in most pedigrees, a hypothesis supported by the birth of a male infant to a mother with PH, who shared her affected haplotype, and who died postnatally of severe, widespread haemorrhage [10]. Cardiovascular or gut malformations might also account for prenatal male lethality [11].

Heterozygous females have normal to borderline intelligence and epilepsy ranging in severity from mild to intractable, with the age at onset usually in the mid teens. A few living male patients with bilateral PNH due to FLNA mutations are on record [10, 11]. Mild missense mutations or mosaic mutations, probably causing limited functional defect of the Filamin A protein, account for survival of affected males [11] who may in turn transmit their genetic defect. Rare patients of both genders with FLNA mutations had unilateral PNH [8, 11].

Other genes may cause bilateral PNH in both genders. A rare recessive form of PNH due to mutations of the ADP-ribosylation factor guanine nucleotide exchange factor-2 (ARFGEF2) has been reported in two consanguineous pedigrees [23]. This gene encodes for the protein brefeldin A (BFA)-inhibited GEF2 (BIG2), which is required for vesicle and membrane trafficking from the trans-Golgi network. Impaired vesicle trafficking prevents transport to the cell surface of polarized mole-

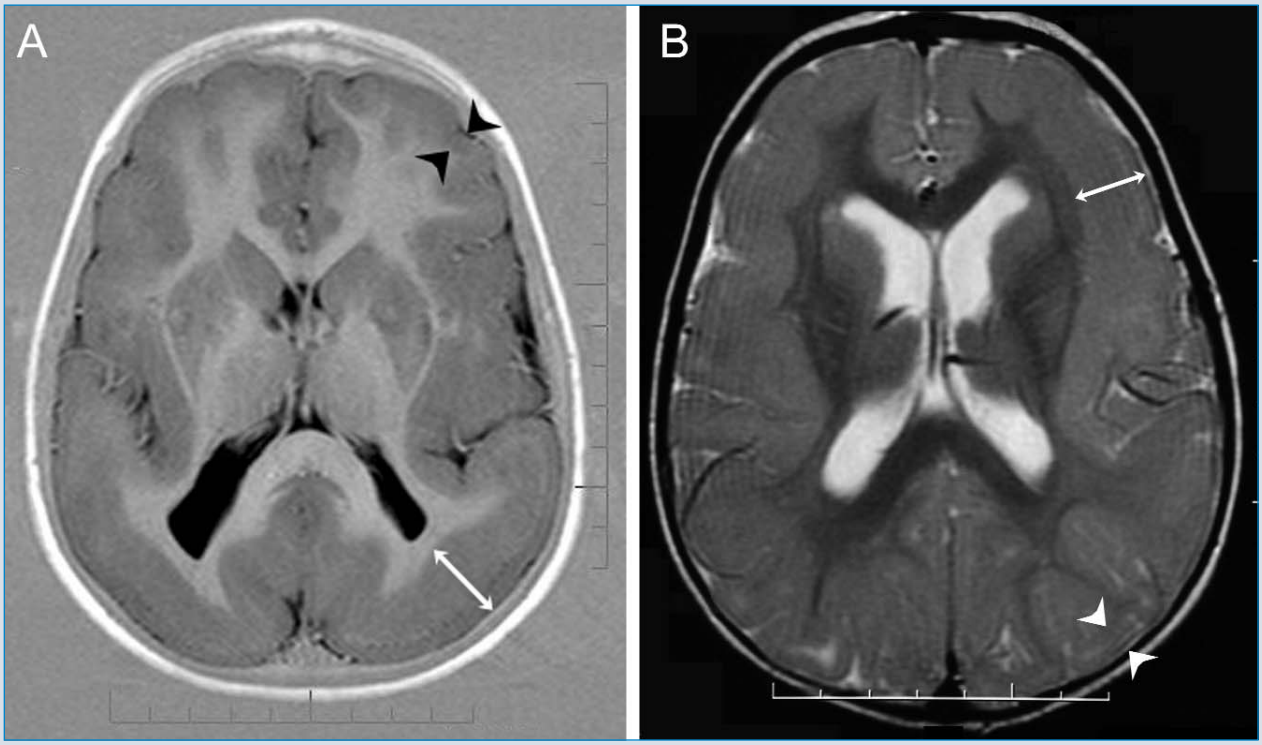

Figure 2: (A) Brain MRI scan; axial section: classical lissencephaly in a boy with LIS1 gene mutation. There is a typical posterior > anterior malformative pattern with relative preservation of the gyral pattern and cortical thickness in the anterior brain; cortical thickness is around 6 mm in the frontal lobes (black arrows; normal cortical thickness = 4 mm) and around 3 cm in the posterior brain (white arrow). (B) Brain MRI scan; axial section: lissencephaly in a girl with DCX mutation. There is a typical anterior > posterior malformative pattern, cortical thickness is around 2 cm in the frontal lobes (single white arrow) and around 4 mm in the posterior brain (double white arrows).

cules such as E-cadherin and b-catenin, whereby disrupting proliferation and migration during cortical development. Affected children had microcephaly, severe developmental delay and early onset seizures, including infantile spasms. Several other sporadic syndromes with bilateral PNH and mental retardation have been described [24-26, 6]. In some such syndromes the malformation may result from small chromosomal rearrangements involving the *FLNA* gene [27] and other unknown genes [28].

Approximately 90% of patients with periventricular nodular heterotopia have epilepsy [29], which can begin at any age. Studies with depth electrodes have provided evidence that seizure activity may arise from periventricular heterotopic cortex [30].

Early Positron Emission Tomography (PET) imaging studies using 2-[(18) F] fluoro-2-deoxy-D-glucose (FDG) showed that heterotopia has the same metabolic activity as normal grey matter [31]. fMRI studies suggest that PNH caused by FLNA mutations may also be functionally integrated in motor circuits, suggesting that neurons that have failed to migrate have maintained the information that allows them to assemble in functionally active aggregates and to participate in integrated networks [32].

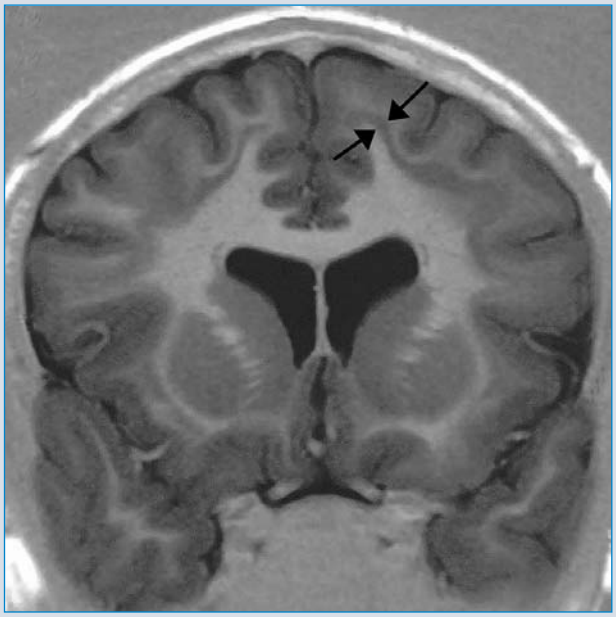

Figure 3: Brain MRI scan; coronal section: young woman with a missense mutation of the DCX gene. The gyral pattern of the cortex looks normal but beneath the cortex, and separated from it by a thin layer of white matter, is present a subcortical laminar (band) heterotopia (black arrow) showing the same signal intensity as the cortex. The thickness of the heterotopic band is variable from about 3 mm to 1 cm.

Classical lissencephaly and subcortical band heterotopia (the agyria-pachygyria-band spectrum) and lissencephaly with cerebellar hypoplasia

Classical Lissencephaly (LIS) and Subcortical Band Heterotopia (SBH) are related cortical malformations secondary to abnormal migration of neurons during early brain development. Lissencephaly is characterized by absent (agyria) or decreased (pachygyria) convolutions, producing a smooth cerebral surface [1]. In lissencephaly, neurons migrate only partially toward their proper cortical destination so that in the mature cortex gyri and sulci fail to form. Subcortical band heterotopia (SBH) is a related disorder in which there are bilateral bands of grey matter found interposed in the white matter between the cortex and the lateral ventricles [33]. The overlying cortex is usually normal with the exception of shallow sulci.

Two genes have been associated with classical LIS and SBH. The first gene – LIS1 (OMIM: #601545) on chromosome 17p13.3 – is responsible for the autosomal form of lissencephaly [34], while the second gene – doublecortin (*DCX or XLIS*) (OMIM: #300067) – is X-linked [35, 36]. Although mutations in either genes can result in either LIS or SBH, the majority of cases of classical LIS are due to deletions or mutations of the LIS1 gene [37-39], whereas the majority of cases of SBH are due to mutations of the DCX gene [35, 36]. LIS1 gene mutations result in LIS more severe in posterior brain regions (the p>a gradient), whereas DCX mutations result in LIS more severe in anterior brain regions (the a > p gradient) [39, 40] (**Figure 2A and 2B**). Among all the patients with isolated LIS, 40% exhibit a deletion involving the entire gene [41], and 25% show an intragenic mutation (4% gross rearrangement, 17% deletion/truncating mutations, 4% missense mutations) [42]. Patients with missense mutations generally have less severe malformations and may accordingly present with much milder neurological and cognitive impairment [42]. Severe truncating mutations cause severe lissencephaly, while milder mutations, usually missense mutations cause pachygyria and rare cases of SBH [43]. Mosaic mutations of LIS1 also cause SBH in the posterior brain [44]. LIS1 gene is also responsible for all cases of Miller-Dieker lissencephaly, which is caused by large deletions of LIS1 and contiguous genes [37]. Deletion of the 14-3-3 epsilon gene located within the 17p13.3 region and about 40 kb telomeric to LIS1, appears to have a role in causing the severe lissencephaly in Miller Dieker syndrome [45].

LIS1 encodes a protein that is similar to the b subunit of heterotrimeric G proteins functions as a regulatory subunit of platelet-activating factor acetylhydrolase (PAF-AH), an enzyme that degrades the bioactive lipid PAF [46]. A reduction in the migration of cerebellar granule cells *in vitro* occurred on treatment with a PAF agonist [47], implying that LIS1 protein function in PAF-AH is related to its essential role in migration. LIS1 pro-

tein has been shown to colocalize with microtubules and to promote their stabilization [48], and an ortholog of LIS1 in Aspergillus nidulans, nudF, mediates nuclear translocation, probably by interacting with microtubules [49]. Thus, LIS1 protein might exert its effects on migration through microtubules.

DCX mutations classically cause striking, double cortex phenotype, in which a second band of cortical neurons exists within the white matter below the true cortex (**Figure 3**). Women with DCX mutations have anteriorly predominant band/pachygyria. However, rare carrier women harbouring missense mutations with normal brain MRI due to either favourable X-inactivation skewing or to mutations having mild functional consequences have been described [50].

Mutations of the coding region of DCX were found in all reported pedigrees including families in which female patients have SBH and male patients have LIS, and in approximately 80% of sporadic female cases and 25% of sporadic male cases of SBH [51]. Maternal germline or mosaic DCX mutations may occur in about 10% of cases of either SBH or XLIS [52]. Hemizygous males with DCX mutations have classical lissencephaly [53] but rare boys with missense DCX mutations with an anteriorly predominant SBH have also been described [50]. The interaction of both DCX and LIS1 with microtubules may explain the striking similarities between the lissencephalic phenotypes produced by mutations in these two genes.

Lissencephaly with agenesis of the corpus callosum and rudimentary dysplastic cerebellum may represent a subset of lissencephaly with cerebellar hypoplasia (LCH) [54]. In 2000 Hong et al. studied two consanguineous pedigrees with an autosomal recessive form of lissencephaly associated with severe abnormalities of the cerebellum, hippocampus, and brainstem [55]. The disorder was mapped to 7q22, and mutations were identified in the *RELN* gene [55] (OMIM #257320). RELN encodes a large (388 kD) secreted protein that acts on migrating cortical neurons by binding to the very low density lipoprotein receptor (VLDLR), the apolipoprotein E receptor 2, alpha3beta1 integrin and protocadherins [56]. There are also data indicating genetic and biochemical interaction between the reelin signalling pathway and Lis1 in the mice [57]. In the reeler mouse mutant (Reln(rl)) Reln mutations cause cerebellar hypoplasia, abnormal cerebral cortical neuronal migration and abnormal axonal connectivity [58]. Neurons in affected mice fail to reach their correct locations in the developing brain, disrupting the organization of the cerebellar and cerebral cortices and other laminated regions. Thus, reelin is thought to control cell-cell interactions critical for cell positioning in the brain.

In 2005 Boycot et al. identified a homozygous deletion encompassing the VLDLR gene in affected individuals non progressive ataxia, mental retardation associated with inferior cerebellar hypoplasia and mild cerebral gyral simplification in the Hutterite population [59]. VLDRL is part of the reelin signalling pathway, therefore it is not surprising that the phenotype in these patients is very similar to LCH.

Lissencephaly is associated with severe mental retardation, epilepsy, and motor disability. Seizures occur in over 90% of children, with onset before age 6 months in about 75%. About 80% have infantile spasms, although the EEG may not show typical hypsarrhythmia. SBH generally has milder clinical sequelae including seizures and mild-to-moderate intellectual disability. Cognitive function correlates with the thickness of the band and degree of pachygyria [37, 33]. Less severe phenotypes of both of these disorders have also been reported [60, 43]. Epilepsy is present in almost all patients with SBH and is intractable in about 65% [61].

X-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia (XLAG)

X-linked lissencephaly with absent corpus callosum and ambiguous genitalia is a severe malformation syndrome that is only observed in boys. The anatomoclinical spectrum includes lissencephaly with posterior-to-anterior gradient and only moderate increase of the cortical thickness (only 6-7 mm in XLAG, versus 15-20 mm seen in classical lissencephaly associated with mutations of LIS1 or DCX), absent corpus callosum, poorly delineated and cavitated basal ganglia, postnatal microcephaly, neonatal-onset epilepsy, hypothalamic dysfunction including deficient temperature regulation, chronic diarrhoea, and ambiguous genitalia with micropenis and cryptorchidism [62, 63]. Early death is not un-

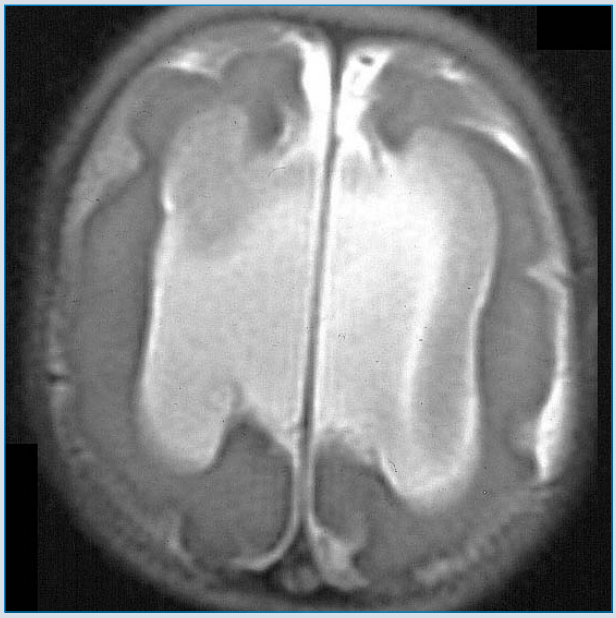

Figure 4: Brain MRI scan; axial section. 1 year-old boy with X-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia due to mutation of the ARX gene. Note absence of the corpus callosum with ventriculomegaly and lissencephaly.

common [64]. Brain neuropathology reveals an abnormally laminated cortex exclusively containing pyramidal neurons, with a pattern suggesting disruption of both tangential and radial migration, dysplastic basal ganglia, hypoplastic olfactory bulbs and optic nerves, abnormal gliotic white matter containing numerous heterotopic neurons, and complete agenesis of the corpus callosum without Probst bundles [63].

Mutations of the X-linked aristaless-related homeobox gene (ARX) (OMIM#300382) were identified in individuals with XLAG (**Figure 4**) and in some female relatives [65]. Females carrying ARX usually have normal cognitive level and may either have normal brain MRI scan or show partial or complete agenesis of the corpus callosum. However, mild mental retardation and epilepsy has been reported in rare female carriers [63]. Mouse Arx and human ARX are expressed at high levels in both dorsal and ventral telencephalon, including the neocortical ventricular zone and germinal zone of the ganglionic eminence, with less intense signals in the subventricular zone, cortical plate, hippocampus, basal ganglia and ventral thalamus [65, 66]. Arx deficient mice show deficient tangential migration and abnormal differentiation of interneurons containing gamma-aminobutyric acid (GABAergic interneurons) in the ganglionic eminence and neocortex. These characteristics recapitulate some of the clinical features of XLAG in humans [65] and might account for the severe neonatal epileptic encephalopathy with suppression burst EEG that is often observed in affected boys.

The mutations of the ARX gene in XLAG patients are in prevalence premature termination mutations (large deletions, frameshift, nonsense mutations, splice site mutations). Missense mutations are less common and essentially located in the homeobox domain [64]. Patients carrying nonconservative missense mutations within the homeodomain showed less severe XLAG, while conservative substitution in the homeodomain caused Proud Syndrome (ACC with abnormal genitalia). A non conservative missense mutation near the C-terminal aristaless domain caused unusually severe XLAG with microcephaly and mild cerebellar hypoplasia. ARX mutations are also associated with milder phenotypes without cortical malformations including X linked infantile spasms, Partington's syndrome and X-linked nonsyndromic mental retardation [67].

Malformations due to abnormal cortical organization

Polymicrogyria

Polymicrogyria is characterized by an excessive number of small and prominent convolutions spaced out by shallow and enlarged sulci, giving the cortical surface a lumpy aspect [68]. Cortical infolding and secondary, irregular, thickening due to packing of microgyri are visible on MRI although mild forms are difficult to recognize on neuroimaging [69]. Two histological types are recognized. In unlayered polymicrogyria, the molecular layer is continuous and does not follow the profile of the convolutions, and the underlying neurons have radial distribution but no laminar organization [5]. In four-layered polymicrogyria, there is a layer of intracortical laminar necrosis with consequent impairment of late migration and post migratory disruption of cortical organization (**Figure 5A and 5B**) [70]. The two subtypes do not necessarily have a distinct origin as both may coexist in contiguous cortical areas [70].

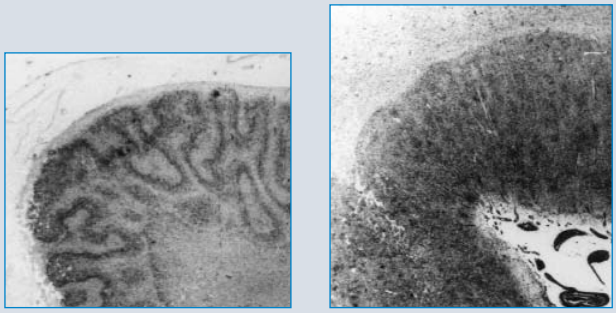

Figure 5: (A) Typical four layered polymicrogyria in the temporal cortex (cresyl violet). Note microgyri with fused molecular layers. (B) On further magnification the thickness of the cortex appears irregular and normal horizontal six layered structure is lost (cresyl violet).

Polymicrogyria can be focal or diffuse, unilateral or bilateral. It can occur as an isolated lesion, in association with other brain malformations such as heterotopia [71] or white matter lesions, or as part of several multiple congenital anomaly/mental retardation syndromes. The extent of polymicrogyria varies from focal polymicrogyria in otherwise normal brain to diffuse polymicrogyria with multiple other brain abnormalities. Similarly, the spectrum of clinical manifestations ranges from normal individuals with only selective impairment of cognitive function [72] and no or easily controlled epilepsy to patients with severe encephalopathies and intractable epilepsy [69]. Several syndromes featuring bilateral polymicrogyria have been described, including bilateral perisylvian polymicrogyria [73] (**Figure 6A**), bilateral parasagittal parietooccipital polymicrogyria [74] (**Figure 6B**), bilateral frontal [75] and frontoparietal polymicrogyria (**Figure 7**) and unilateral perisylvian (**Figure 6C**) or multilobar polymicrogyria [69]. These different forms might represent distinct entities that reflect the influence of regionally expressed developmental genes. In some children with unilateral or bilateral perisylvian polymicrogyria, electrical status epilepticus during sleep can develop [76].

Bilateral perisylvian polymicrogyria involves the grey matter bordering the sylvian fissure bilaterally that are often more vertically oriented and extend more posteriorly up to the parietal lobes compared with normal con-

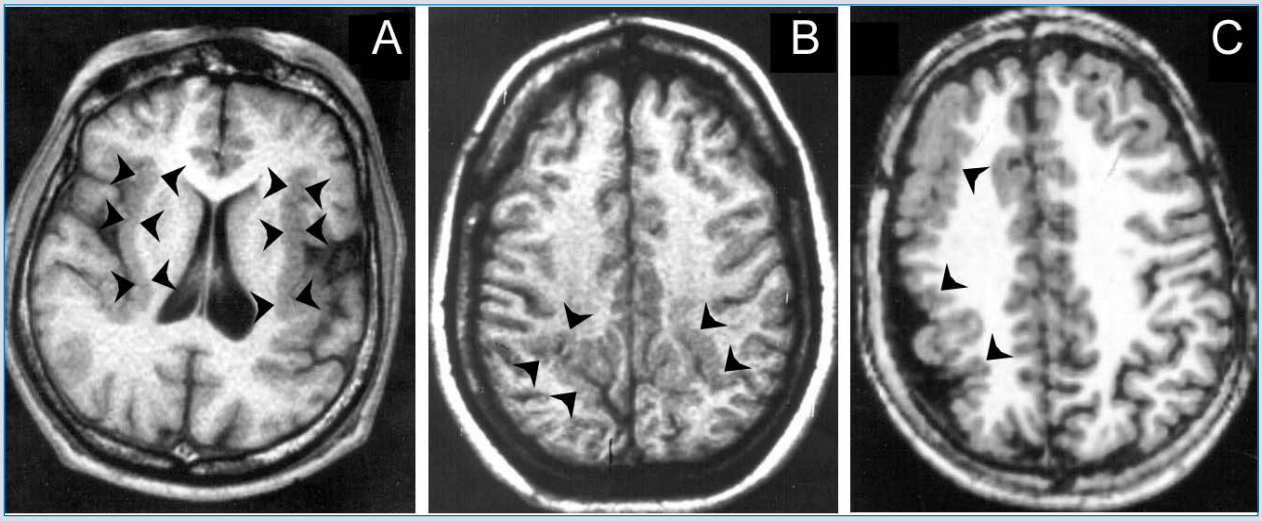

Figure 6: (A) Brain MRI; T1weighted axial section. Bilateral perisylvian polymicrogyria. Sylvian fissures are open and the perisylvian cortex is thickened and irregular (black arrows). Young man with Lennox–Gastaut syndrome. (B) Brain MRI; T1weighted axial section. Bilateral parasagittal polymicrogyria. Irregular thickening and infolding of the cortex at the mesial parieto-occipital junction (black arrows). Young girl with intractable partial epilepsy. (C) Brain MRI; T1 weighted axial section. Unilateral polymicrogyria. The right hemisphere is smaller than the left and the subarachnoid space overlying the right hemisphere is enlarged (black arrows). The cortex on the right is irregular, with areas of thickening. Eight-year-old boy with left hemiparesis, moderate mental retardation, atypical absences and partial motor seizures.

trols (**Figure 6A**). The abnormality is usually symmetrical but varies in extent among patients. Both four-layered polymicrogyria and unlayered polymicrogyria have been observed [77, 73, 26]. Although most patients are sporadic, several familial cases have been reported, with possible autosomal recessive, autosomal dominant, X-linked dominant and X-linked recessive inheritance [78]. A locus for X-linked bilateral perisylvian polymicrogyria maps to Xq28 in some families [79]. Bilateral perisylvian polymicrogyria has also been reported in some children with 22q11.2 deletion [80, 81] and in children born from monochorionic biamniotic twin pregnancies which were complicated by twin-twin transfusion syndrome [82, 83], confirming causal heterogeneity.

Bilateral perisylvian polymicrogyria has been described in a male patient with severe neonatal encephalopathy whose sister had classical features of Rett syndrome. Both patients had a mutation in the methyl-CpG binding protein 2 (MECP2) gene on Xq28, suggesting that MECP2 screening could be considered in males with severe neonatal encephalopathy and in males and females with bilateral polymicrogyria [84]. The paired-box transcription factor, PAX6, is a highly conserved developmentally regulated gene on 11p13 encoding for a transcription factor. Murine models suggest that PAX6 plays a role in human brain development. Bilateral polymicrogyria occurs in homozygous mutant mice. Unilateral polymicrogyria was demonstrated in a mother and son with mutations in the PAX6 gene, making this a candidate gene for polymicrogyria [85]. A single sibship has been reported in which the female proband presented with polymicrogyria, dysmorphic features, and raised lactic acid. Her elder brother presented with typical mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome. Both were carriers of the A3243G mutation on mitochondrial transfer RNA for the leucine 1 (MTTL1) gene [86].

Patients with bilateral perisylvian polymicrogyria have facio-pharingo-glosso-masticatory diplegia [87] and dysarthria. Most have mental retardation and epilepsy. Those with more extensive damage may have spastic quadriparesis [69]. Seizures usually begin between age 4 and 12 years and are poorly controlled in about 65% of patients.

Bilateral frontal polymicrogyria was described in children with developmental delay, mild spastic quadriparesis and epilepsy [75]. Although most reported cases were sporadic, occurrence in offspring of consanguineous parents and in sibblings, was considered suggestive of autosomal recessive inheritance. Indeed, frontoparietal polymicrogyria a malformation only extending a few centimeters further back in the parietal lobes (**Figure 7**), was reported in several consanguineous and non-consanguineous families with recessive pedigrees and was initially mapped to chromosome 16q12.2-21 [88] and subsequently associated with mutations of the G protein-coupled receptor gene 6 (GPR56) [89]. GPR56 belongs to the G-protein-coupled receptor family, the largest gene family in the human genome, representing about 1% of all genes. The pattern of expression of mouse Gpr56 as well as the topography of the cortical abnormality in patients harbouring homozygous mutations strongly suggests that Gpr56 regulates cortical patterning [89]. The fact that the N-terminus domain

that defines GPR56 is unique to animals that have a cerebral cortex also suggests that this gene might have been a target in the evolution of the cerebral cortex [89]. Epilepsy, seen in the majority of patients, was mainly accompanied by partial seizures and atypical absences and was of variable severity.

Several chromosomal abnormalities have been associated with focal or diffuse, unilateral or bilateral polymicrogyria therefore, high resolution karyotyping or microarray based comparative genomic hybridisation (CGH) should be carried out to identify possible chromosomal abnormalities [90].

Schizencephaly

Schizencephaly (cleft brain) consists of a unilateral or bilateral full thickness cleft of the cerebral hemispheres with communication between the ventricle and extra-axial subarachnoid spaces. The walls of the clefts may be widely separated or closely adjacent, bilateral clefts are usually symmetric [91]. The clefts are most often found in the perisylvian area [92]. The cortex surrounding the cleft is polymicrogyric, for this reason schizencephaly is considered a disorder of cortical organization [93]. However, an abnormal proliferation of the neuronal precursor is also possible, especially when open lip clefts, with absence of development of a large part of one cerebral hemisphere, are considered. Schizencephaly may be due to regional absence of proliferation of neurons and glia or to abnormal cortical organization. Local failure of induction of neuronal migration or focal ischemic necrosis with destruction of the radial glial fibres during early gestation, have been hypothesized [5]. Although schizencephaly is usually sporadic, familial occurrence has been reported [94]. Several sporadic patients and two siblings of both genders harbouring germline mutations in the empty spiracles homeobox gene EMX2 have been described [95, 96]. However, the role of the EMX2 gene and the pattern of inheritance are still unclear. Clinical findings include focal seizures in most patients (about 80% of cases in one large review) [96], usually beginning before age 3 years in bilateral cases. Bilateral clefts are associated with microcephaly, severe delay and spastic quadriparesis whereas patients with unilateral schizencephaly most often have hemiparesis or may be brought to medical attention after seizure onset without having any other neurological abnormality [97].

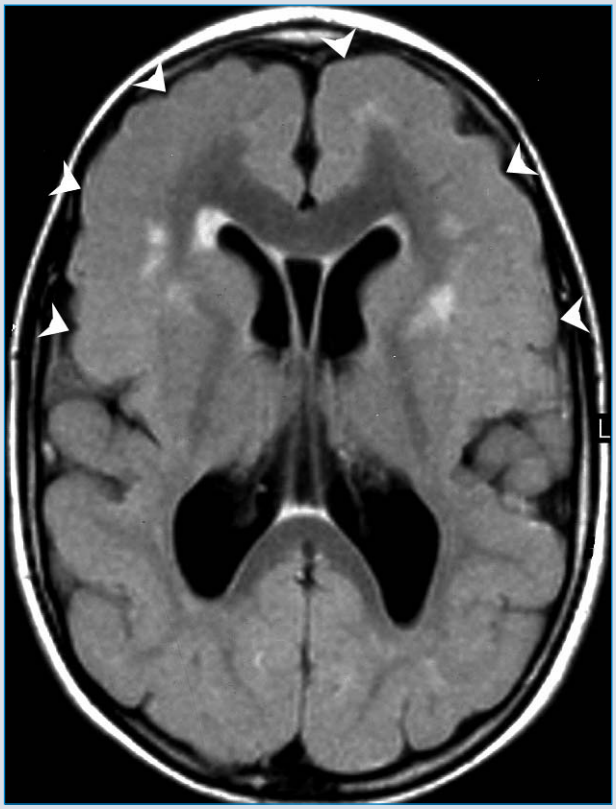

Figure 7: Brain MRI; T1 weighted axial section, bilateral frontoparietal polymicrogyria (black arrows) in a girl with the GPR56 gene mutation and Lennox-Gastaut syndrome.

Conclusions

Linkage studies and positional cloning have shed light on the genetic basis of some malformations of the cerebral cortex. Genetic heterogeneity is present and the genes so far identified that are associated with a specific type of malformation of cortical development account for most but not all patients with the corresponding malformative pattern. Similarly, identical malformative patterns may be caused by mutations of different genes that function in the same molecular pathway as the 'founding' gene associated with the phenotype. Most of the identified genes encode for proteins expressed in the brain whose function in the proliferation, apoptosis and migration of neurons is yet to be fully elucidated. Further elucidation of the cellular and molecular events underlying cortical development will come mainly from animal studies, which are amenable to experimental approaches, including the induction of genetic mutations. Intractable epilepsy is common in some cortical malformations but the mechanisms contributing to epileptogenesis are currently poorly understood.

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