Topical Review

Neuronal Migration Disorders, Genetics, and Epileptogenesis

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ABSTRACT

Several malformation syndromes with abnormal cortical development have been recognized. Specific causative gene defects and characteristic electroclinical patterns have been identified for some. X-linked periventricular nodular heterotopia is mainly seen in female patients and is often associated with focal epilepsy. FLN1 mutations have been reported in all familial cases and in about 25% of sporadic patients. A rare recessive form of periventricular nodular heterotopia owing to ARGEF2 gene mutations has also been reported in children with microcephaly, severe delay, and early-onset seizures. Lissencephaly-pachygyria and subcortical band heterotopia represent a malformative spectrum resulting from mutations of either the LIS1 or the DCX (XLIS) gene. LIS1 mutations cause a more severe malformation posteriorly. 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 male patients and subcortical band heterotopia in female patients. Mutations of the coding region of DCX were found in all reported pedigrees and in about 50% of sporadic female patients with subcortical band heterotopia. Mutations of XLIS have also been found in male patients with anterior subcortical band heterotopia and in female patients with normal brain magnetic resonance imaging. The thickness of the band and the severity of pachygyria correlate with the likelihood of developing severe epilepsy. 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 infantile spasms with suppression-burst electroencephalograms. Early death is frequent. Carrier female patients can have isolated corpus callosum agenesis. Schizencephaly has a wide anatomoclinical spectrum, including focal epilepsy in most patients. Familial occurrence is rare. Initial reports of heterozygous mutations in the EMX2 gene have not been confirmed. 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. (J Child Neurol 2005;20:287–299).

Genetic malformations of the cerebral cortex are usually characterized by malposition and faulty differentiation of gray matter.1 Epilepsy is often present and tends to be severe, although its incidence and type vary in different malformations.2 It is estimated that up to 40% of children with drug-resistant epilepsy have a cortical malformation.3 Mutations of several genes regulating brain development have been associated with specific malformations.1

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.4 Disorders affecting neuronal migration are characterized by abnormal neuronal positioning.4 When migration is arrested during later cortical development, abnormal cell position is more likely to be restricted to the cortex. In the following sections, we discuss the most frequent cortical malformations causing epilepsy and those for which the causative genes have been cloned.
MALFORMATIONS RELATED TO ABNORMAL PROLIFERATION OF NEURONS AND GLIA

Hemimegalencephaly

In hemimegalencephaly, one cerebral hemisphere is enlarged and presents with a thick cortex, wide convolutions, and reduced sulci (Figure 1). Although the abnormality is strictly unilateral in most cases,1 postmortem examination showed minor abnormalities of the apparently unaffected hemisphere in two cases and mild cortical dysplastic abnormalities in another.5,6 The potential for structural changes in the seemingly normal hemisphere is of particular importance with respect to planning surgical treatment of epilepsy. Laminar organization of the cortex is absent, and gray-white matter demarcation is poor. Giant neurons are observed throughout the cortex and the underlying white matter. In about 50% of cases, large, bizarre cells are observed, which have been named balloon cells.4,5 In some patients, the structural abnormality is multifocal, usually predominating in the posterior quadrant (posterior temporal and parieto-occipital lobes), but does not affect an entire hemisphere.7 Hemimegalencephaly is probably an etiologically heterogeneous condition. Localization of the abnormality to one cerebral hemisphere and the fact that the malformation has always been sporadic can indicate somatic mosaicism.4 It has also been suggested that a fault in programmed cell death can be a causative factor.8

Hemimegalencephaly has been described in the context of different disorders, including epidermal nevus syndrome, Proteus syndrome, hypomelanosis of Ito, neurofibromatosis type 1, and tuberous sclerosis, but occurs most frequently as an isolated malformation. The clinical and anatomic spectrum of severity is wide, ranging from severe epileptic encephalopathy beginning in the neonatal period to patients with normal cognitive function.9,10 Indeed, the milder end of the clinical spectrum includes patients with well-controlled seizures or no seizures at all.11 However, most patients have a severe structural abnormality and almost continuous seizures. The most common presentation is asymmetric macrocrania, hemiparesis, hemianopia, mental retardation, and seizures. The electroclinical features usually include partial motor seizures beginning in the neonatal period, infantile spasms, and often an asymmetric suppression-burst pattern on sleep electroencephalography (EEG).11,12 Patients with early-onset, severe epilepsy almost always develop major cognitive and motor impairment.13 In addition, there is a high mortality rate in the first months or years of life, with status epilepticus being the most important cause of death.14-16 Seizure intractability in these patients can usually be established within the first year of life.11,17 This is important because major surgical procedures can stop life-threatening seizures and prevent epileptic activity from interfering with physiologic activity of the contralateral, healthy hemisphere.16,17 There are indications that the operation should be performed early19 because in younger children, transfer of functions to the “normal” hemisphere is greater and a better neuropsychologic outcome is more likely,19 younter children, transfer of functions to the “normal” hemisphere (Figure 2).20-22

Focal Cortical Dysplasia

Focal cortical dysplasia was originally described in patients who were treated surgically for drug-resistant epilepsy.23 The histologic abnormalities are usually restricted to one lobe or a smaller segment and include local disorganization of the laminar structure, large aberrant neurons, isolated neuronal heterotopia in subcortical white matter, balloon cells, giant and odd macroglia, foci of demyelination, and gllosis of adjacent white matter.24 The abnormal area is not usually sharply delimited from adjacent tissue.4,25 One or more of the above components might not be present, and three main subtypes of focal cortical dysplasia are recognized, which might correspond to the different times of embryologic origin.26 A first type is characterized by architectural dysplasia, with abnormal cortical lamination and ectopic neurons in the white matter. A second type, defined as cytoarchitectural dysplasia, is characterized by giant neurofilament-enriched neurons in addition to altered cortical lamination. A third type, corresponding to Taylor-type cortical dysplasia, is characterized by giant dysmorphic neurons and balloon cells associated with cortical lamination disruption. Patients with architectural dysplasia have lower seizure frequency than those with cytoarchitectural and Taylor-type dysplasia.25 Focal cortical dysplasia can occur in any part of the cortex. The lesion can be quite extensive, rendering complete removal impossible in many cases.25,26 Magnetic resonance imaging (MRI) can be unrevealing in up to 34% of patients.24 Distinctive signal alterations on T2-weighted or fluid-attenuated inversion recovery images are present in most patients with Taylor-type dysplasia, often associated with focal areas of cortical thickening, simplified gyration, blurring of the gray-white limit, or rectilinear boundaries between gray and white matter (Figure 2).24,28,29 Focal hypoplasia with MRI abnormalities is often found in architectural dysplasia.24 The histologic characteristics of Taylor-type dysplasia are indistinguishable from those of hemimegalencephaly. Some cases present involvement of more than an entire lobe and probably represent a continuum with minor forms of hemimegalencephaly.

Focal cortical dysplasia usually presents with intractable focal epilepsy, which can start at any age but generally before the end of adolescence. Seizure semiology depends on the location of the lesion, and focal status epilepticus has been reported fre-
owing to the distinctive interictal epileptiform discharges,30 which may be better defined in patients with Taylor-type dysplasia, possibly using immunocytochemistry.33,41 Such abnormal circuitry can play a role in the genesis of epileptiform activity.32–35 Unless the dysplastic area is large, patients do not suffer from severe neurologic deficits. Interictal EEG shows focal, rhythmic epileptiform discharges in about half of the patients.36 The ictal EEG abnormalities are highly specific for focal cortical dysplasia, are located over the epileptogenic area, and correlate with the continuous ictal discharges recorded during electrocorticography.30,37,38 Electrocorticographic seizure activity shows spatial colocalization with the lesion. Complete resection of the tissue producing ictal electrocorticographic discharges is essential for good seizure outcome. Intrinsic epileptogenicity of the dysplastic tissue has been confirmed with depth electrode studies.31

The mechanisms underlying the ictal activity generated by dysplastic neocortex remain to be elucidated. In the abnormal cortical multilaminar organization typical of focal cortical dysplasia, neurons are prevented from establishing normal synaptic connections with their neighbors and are dysfunctional. Intra-cellular recordings from neurons of a dysplastic human neocortex have revealed no abnormalities in the membrane properties of single neurons.30,35 However, a dysfunction of synaptic circuits seems to be responsible for the abnormal synchronization of neuronal populations underlying the genesis of epileptiform activity. Abnormalities in the morphology and distribution of local-circuit γ-aminobutyric (GABA)ergic inhibitory neurons have been observed using immunocytochemistry.33,34 Such abnormal circuitry can play an important role in originating and maintaining the epileptiform activity.32

The interictal EEG shows focal, often rhythmic epileptiform discharges in about half of the patients.36 Most patients with electrocorticographic ictal discharges who had complete removal of the discharging tissue were seizure free or had over 90% reduction in major seizures. None of the patients with persistence of discharging tissue had a favorable outcome.30 The different histologic subtypes of focal cortical dysplasia can carry different chances of seizure freedom after surgery. According to Tassi et al, who used depth electrodes in most cases, patients with Taylor-type dysplasia had the best outcome, with 75% being seizure free (Engel class Ia) compared with 50% with cytoarchitectural dysplasia and 43% with architectural dysplasia.24 In fact, the area of resection could be better defined in patients with Taylor-type dysplasia, possibly owing to the distinctive interictal epileptiform discharges,33 which can be captured by depth electrodes.32

Most descriptions of focal cortical dysplasia and hemimegalencephaly are based on studies from epilepsy surgery centers. Thus, the clinical and electrophysiologic features described are likely to be typical only of the most severe cases. Our experience indicates that there are some patients with well-controlled seizures in whom MRI shows focal abnormalities identical to those present in patients with histologically proven focal cortical dysplasia.43

MALFORMATIONS OWING TO ABNORMAL NEURONAL MIGRATION

Periventricular Nodular Heterotopia

Periventricular nodular heterotopia, which is often bilateral, consists of confluent nodules of gray matter located along the lateral ventricles. Although most patients with periventricular nodular heterotopia are brought to medical attention because they have epileptic seizures without additional neurologic abnormalities, the spectrum of clinical presentations is wide. There is some correlation between the size of periventricular nodular heterotopia and the severity of clinical impairment. However, the degree of anatomic and functional impairment of the cerebral cortex overlying the area(s) of heterotopia is variable and can, in turn, contribute to determining the clinical picture.

Periventricular nodular heterotopia occurs much more frequently in women as X-linked bilateral periventricular nodular heterotopia (Figure 3A) (Mendelian Inheritance in Man #300049), which is associated with prenatal lethality in almost all men44,45 and a 50% recurrence risk in the female offspring of affected women. Almost 100% of families with X-linked bilateral periventricular nodular heterotopia and about 20% of sporadic patients (19% of sporadic women and 19% of sporadic men) harbor mutations of the filamin 1 gene (FLN1),44–47 The low percentage of FLN1 mutations in sporadic cases could be explained by low somatic mosaicism,46 as well as the viability of some affected males. FLN1 maps to chromosome Xq28, is composed of 48 exons, spans a 26 kb genomic region, and codes for filamin1, a 280 kDa protein with three major functional domains, allowing homodimerization and binding to actin and a wide range of cytoplasmic signaling proteins.46

Heterozygous females have normal to borderline intelligence and epilepsies of variable severity. Coagulopathy and cardiovascular abnormalities have been observed in some patients.46 A few living male patients with bilateral periventricular nodular heterotopia owing to FLN1 mutations are on record.46,47 Mild missense mutations or mosaic mutations, probably causing limited functional defect of the FLN1 protein, account for survival of affected men,47 who can, in turn, transmit their genetic defect. Rare patients of both genders with FLN1 mutations had unilateral periventricular nodular heterotopia.47,48
Other genes can cause bilateral periventricular nodular heterotopia in both genders. A rare recessive form of periventricular nodular heterotopia owing to mutations of the adenosine diphosphate–ribosylation factor guanine nucleotide exchange factor 2 (ARFGEF2) has been reported in two consanguineous pedigrees. This gene encodes for the protein brefeldin A–inhibited guanine nucleotide exchange factor 2 (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 molecules, such as E-cadherin and β-catenin, thereby disrupting proliferation and migration during cortical development. Affected children had microcephaly (Figure 3B), severe developmental delay, and early-onset seizures, including infantile spasms. Several other sporadic syndromes with periventricular nodular heterotopia and mental retardation have been described, almost exclusively in boys. In some such syndromes, the malformation can result from small chromosomal rearrangements involving the FLN1 gene and other unknown genes.

Genetic counseling is relatively easy in familial cases with a clear X-linked pattern of inheritance. Classic periventricular nodular heterotopia with cerebellar hypoplasia and no dysmorphic features is much more frequent in women and more likely to be due to FLN1 mutations than in atypical cases. Among carrier women, about half have de novo mutations of FLN1, whereas the remaining half have inherited mutations. Although maternal transmission is much more likely, father-to-daughter transmission is possible, implying that either parent can transmit the mutation to a female proband. An affected man with periventricular nodular heterotopia caused by the FLN1 mutation would be expected to transmit the mutation to all of his daughters, unless somatic mosaicism is present. If none of the parents has epilepsy or cognitive impairment, the proband’s mother should be studied first to confirm the mutation or the brain abnormality. If the mother is mutation negative and the proband is a female, the father should also be studied. Given that germline mosaicism of FLN1 has never been reported in periventricular nodular heterotopia, the recurrence risk (for other children) seems to be very low when a mutation is found in the proband but neither parent is a carrier.

Approximately 90% of patients with periventricular nodular heterotopia have epilepsy, which can begin at any age. Dubeau et al studied 33 patients with periventricular and subcortical nodular heterotopia, 29 (88%) of whom had seizures, mainly partial attacks with temporoparieto-occipital auras. Seizures began between the age of 2 months and 33 years and were intractable in 27 patients (82%). Bilateral periventricular nodular heterotopia was observed in nine patients. Temporal lobectomy, which did not include the area of heterotopia in seven patients, did not result in any significant improvement, despite EEG findings in the temporal area. Studies with depth electrodes have provided evidence that seizure activity can arise simultaneously from periventricular heterotopic cortex and from distantly located cortical areas. Surgical removal of the heterotopic cortex, as well as the normal-appearing epileptogenic cortex, led to seizure freedom.

Early fluorodeoxyglucose–positron emission tomographic (PET) studies had shown that heterotopia has the same metabolic activity as normal gray matter. Functional MRI studies suggest that periventricular nodular heterotopia caused by FLN1 mutations can 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.
Classic Lissencephaly and Subcortical Band Heterotopia (Agyria-Pachygyria-Band Spectrum)

Lissencephaly (smooth brain) is characterized by absent (agyria) or decreased (pachygyria) convolutions, producing a smooth cerebral surface. The most frequent forms are caused by mutations of the LIS1 gene (Mendelian Inheritance in Man #601545) and of the DCX (or XLIS) gene (Mendelian Inheritance in Man #300121). Subcortical band heterotopia is a slightly different malformation that is now included within the agyria-pachygyria-band spectrum. In subcortical band heterotopia, the gyral pattern is normal or simplified with broad convolutions and increased cortical thickness. Just beneath the cortical ribbon, a thin band of white matter separates the cortex from a heterotopic band of gray matter of variable thickness and extension. Most cases of subcortical band heterotopia are caused by mutations of the DCX gene and a minority by mutations of the LIS1 gene. Lissencephaly and subcortical band heterotopia caused by mutations of the LIS1 and DCX genes have distinct anatomic features that can help in choosing the diagnostic strategy and are illustrated below.

Several malformation syndromes associated with lissencephaly have been described. The LIS1 gene is the first gene that was associated with human lissencephaly. A morphologic feature that is common to the malformative spectrum caused by LIS1 mutations is a posteriorly predominant brain abnormality. The LIS1 is the gene responsible for all cases of Miller-Dieker lissencephaly, which is caused by large deletions of LIS1 and contiguous genes, for approximately 65% of cases of isolated lissencephaly sequence, and for almost all cases in which the gyral disorder is more severe posteriorly. Among all of the patients with isolated lissencephaly sequence, 40% exhibit a deletion involving the entire gene and 25% show an intragenic mutation (4% gross rearrangement, 17% deletion or truncating mutations, 4% missense mutations). Patients with missense mutations generally have less severe malformations and can, accordingly, present with much milder neurologic and cognitive impairment. Severe truncating mutations cause severe lissencephaly, whereas milder mutations, usually missense mutations, cause pachygyria and rare cases of subcortical band heterotopia. Mosaic mutations of LIS1 cause subcortical band heterotopia in the posterior brain.

DCX mutations usually cause classic lissencephaly in hemizygous males and subcortical band heterotopia in heterozygous females. Mutations of the coding region of DCX were found in all reported pedigrees and in 38% to 91% of sporadic female patients. Rare carrier women harboring missense mutations show normal brain MRI owing to either favorable X-inactivation skewing or to mutations with mild functional consequences. All women with DCX mutations and abnormal MRIs have an anteriorly predominant band or pachygyria. About one fourth of those with an anterior band and all of those with a posteriorly predominant band or a unilateral band have not shown DCX mutations, suggesting that other loci or somatic mosaicism might be responsible for these variable phenotypes. Maternal germline or mosaic DCX mutations can occur in about 10% of cases of either subcortical band heterotopia or XLIS. In boys, the rare cases of subcortical band heterotopia that have been described were associated with missense mutations of DCX when anteriorly predominant or with either missense or mosaic LIS1 mutations when posteriorly predominant.
Classical lissencephaly has a prevalence of 11.7 per million births (1 in 85,470),\textsuperscript{21} but the prevalence of milder phenotypes is unknown. Affected children have early developmental delay and eventual profound mental retardation and spastic quadripareisis. Some children with severe lissencephaly have lived more than 20 years, but their life span is often shorter. Seizures occur in over 90% of children, with onset before 6 months in about 75%. About 80% have infantile spasms,\textsuperscript{2} although the EEG might not show typical hypsarrhythmia. Most children subsequently have multiple seizure types, including persisting spasms, focal seizures, tonic seizures, atypical absences, and atonic seizures.\textsuperscript{74} The EEG demonstrates diffuse, high-amplitude, fast rhythms, which are considered to be highly specific for this malformation.\textsuperscript{75}

The main clinical manifestations of subcortical band heterotopia are mental retardation and epilepsy. Cognitive function ranges from normal to severe retardation and correlates with the thickness of the band and the degree of pachygyria.\textsuperscript{76} Epilepsy is present in almost all patients with subcortical band heterotopia and is intractable in about 65%.\textsuperscript{51} About 50% of epilepsy patients have focal seizures and the remaining 50% have generalized epilepsy, often Lennox-Gastaut syndrome. Those with more severe MRI abnormalities have significantly earlier seizure onset and are more likely to develop Lennox-Gastaut syndrome.\textsuperscript{76} Depth electrode studies demonstrated that epileptiform activity can originate directly from the heterotopic neurons.\textsuperscript{77} Callosotomy has been associated with worthwhile improvement in drop attacks in a few patients.\textsuperscript{75,78} Epilepsy surgery for focal seizures yields poor results.\textsuperscript{79}

**Laboratory Investigations in LIS1 and XLIS**

**Lissencephaly-Pachygyria-Band Heterotopia**

**Chromosome Analysis** A standard blood chromosome analysis (400–550 band resolution) is warranted in all patients with classic lissencephaly. A few cases have been reported of patients with classic lissencephaly owing to a chromosomal reciprocal translocation.\textsuperscript{80–82} About 60% of patients with Miller-Dieker syndrome show a cytogenetically visible deletion, and a few of them show a different chromosome rearrangement (translocation, ring chromosome).

**Fluorescent In Situ Hybridization** Fluorescent in situ hybridization with commercial probes containing the LIS1 gene is required in all patients in whom a chromosome 17 lissencephaly is suspected on the basis of the appearance of the MRI.\textsuperscript{83} About 40% of patients with isolated lissencephaly sequence show a deletion at chromosome 17p13.3. Because these deletions are not observed under a standard chromosome banding analysis, they are referred to as “submicroscopic.” In particular, it is recommended that a fluorescent in situ hybridization study be performed using the LIS1-specific probe PAC 95H6.

**LIS1 Gene Sequencing and Southern Blot Analysis** The analysis consists of the direct sequencing of the LIS1 gene, following polymerase chain reaction amplification of the entire coding region. About 25% of patients with classic lissencephaly show an intragenic mutation of LIS1. Gene sequencing is not 100% sensitive because the promoter and the transcription regulatory regions of the gene are not routinely investigated, and a mutation in these regions could be missed. The Southern blot analysis reveals gross rearrangements of the LIS1 gene, which can be detected in about 4% of patients. The recent demonstration of mosaic mutations of the LIS1 gene in individuals with posterior band heterotopia-pachygyria suggests that a highly sensitive technique, such as denaturing high-pressure liquid chromatography, can be useful in identifying low-level mosaicism, which can escape recognition by direct sequencing or other standard techniques.\textsuperscript{86}

**DCX Gene Sequencing** This analysis is indicated in male individuals with classic lissencephaly in whom an X-linked pattern of inheritance is suspected, on the basis of either pedigree analysis or MRI evidence of a more severe malformation in the frontal brain regions.\textsuperscript{87} Both female and male patients with subcortical band heterotopia should be tested for DCX mutations whenever genetic counseling is advisable. This analysis is performed on the coding exons of the DCX gene that has a high yield,\textsuperscript{84,85} although, similarly to the LIS1 gene sequencing, it does not detect all of the potential causative disease mutations. When a mutation in the DCX gene is found in a child of either gender with XLIS, mutation analysis should be extended to the proband’s mother, even if her brain MRI is normal.\textsuperscript{73} The report of relatively mildly affected male patients carrying missense DCX mutations\textsuperscript{73} makes father-to-daughter transmission theoretically possible, although not yet reported.

**Laboratory Testing Strategy** In patients with classic lissencephaly, the cytogenetic and molecular investigations are part of the diagnostic process, which relies, in addition, on the pedigree analysis, the experience of the examiner of brain MRI and the syndromic evaluation of the child. When Miller-Dieker syndrome is suspected, a standard chromosome
analysis and fluorescent in situ hybridization assay on chromosome 17p13.3 are indicated.\textsuperscript{85} If both tests are normal, the patient is very likely not to be affected with Miller-Dieker syndrome. When nonsyndromic isolated lissencephaly is diagnosed, careful assessment of the anteroposterior gradient of gyral pattern abnormality and cortical thickness will be suggestive of the involvement of either the \textit{LIS1} or the \textit{DCX} gene. When lissencephaly is more severe posteriorly, it is worth performing the chromosome analysis with a fluorescent in situ hybridization assay on chromosome 17p13.3. If a deletion is not found, \textit{LIS1} gene sequencing and the Southern blot analysis should be performed consequently. In boys whose MRI shows more severe pachygyria in the frontal lobes, sequencing of the \textit{DCX} gene is indicated.

Mutations of \textit{LIS1} and \textit{DCX} have been reported in patients with subcortical band heterotopia. The pedigree analysis and assessment of the distribution of the heterotopic band and areas of pachygyria are helpful to predict \textit{DCX} involvement versus the rare cases owing to germline or mosaic \textit{LIS1} mutations. \textit{DCX} mutations should be searched for by direct sequencing. Mutation analysis with direct sequencing of the relevant exons is also indicated in the mothers of patients harboring a \textit{DCX} mutation or other potential female carriers in the family who are of reproductive age. Normal brain MRI does not exclude \textit{DCX} mutations in female carriers.\textsuperscript{71,86}

\textbf{Genetic Counseling}

\textbf{Miller-Dieker Syndrome} About 80\% of patients with Miller-Dieker syndrome have a de novo deletion and 20\% have inherited a deletion from a parent carrying a balanced chromosome rearrangement. For this reason, a karyotype and fluorescent in situ hybridization assay should be obtained from both parents of children with Miller-Dieker syndrome. If the mutation event is de novo, the recurrence risk is low (about 1\%). If one of the parents is a carrier of a chromosomal imbalance, the recurrence risk will be calculated accordingly.

\textbf{\textit{LIS1} Lissencephaly} All reported mutations in the \textit{LIS1} gene (deletion, intragenic, submicroscopic) are de novo. Nevertheless, if a \textit{LIS1} mutation is found, it is correct to perform the mutation analysis on both parents. Given the theoretical risk of germline mosaicism in either parent (which has been demonstrated for other diseases but never for \textit{LIS1} lissencephaly), a couple with a child with chromosome 17 lissencephaly is usually given a 1\% recurrence risk in the offspring.

\textbf{XLIS Lissencephaly} When a mutation in the \textit{DCX} gene is found in a boy with lissencephaly, mutation analysis of \textit{DCX} should be extended to the proband’s mother, even if her brain MRI is normal. If the mother is a mutation carrier, the mutation will be transmitted according to mendelian inheritance. If the mother is not a carrier, she can still be at risk of harboring germline mosaicism,\textsuperscript{44} and the risk of transmitting the mutation to her offspring might roughly be estimated at around 5\%. For this reason, a prenatal diagnosis might be indicated in every pregnancy of a woman who has a child with a \textit{DCX} mutation.\textsuperscript{85}

\textbf{Classic Lissencephaly Without a Detected Mutation} If a mutation is not found in the \textit{LIS1} or \textit{DCX} gene, the anteroposterior lissencephaly gradient detected on MRI might still be helpful in distinguishing the \textit{X}-linked versus the chromosome 17–linked forms or other forms with different anatomic patterns and can be used in the counseling session with the parents of a patient with classic lissencephaly.

\textbf{Autosomal Recessive Lissencephaly With Cerebellar Hypoplasia} Two recessive pedigrees, each with three affected sibs showing moderately severe pachygyria and extremely severe cerebellar hypoplasia, have been associated with a mutation and a deletion of the \textit{reelin} gene.\textsuperscript{87} Affected children in one family had congenital lymphedema, hypotonia, severe developmental delay, and generalized seizures that were controlled by drugs. Severe hypotonia, delay, and seizures were also reported in the other pedigree.

\textbf{X-LINKED LISSENCEPHALY WITH CORPUS CALLOSUM AGENESIS AND AMBIGUOUS GENITALIA} X-linked lissencephaly with absent corpus callosum and ambiguous genitalia is a severe malformation syndrome that is observed only in boys. The anatomo-clinical spectrum includes lissencephaly with a posterior-to-anterior gradient and only a moderate increase in the cortical thickness (only 6 to 7 mm in \textit{X}-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia versus 15 to 20 mm seen in classic lissencephaly associated with mutations of \textit{LIS1} or \textit{DCX}) (Figure 7), an absent corpus callosum, poorly delineated and cavitated basal ganglia, postnatal microcephaly, neonatal-onset epilepsy, hypothalamic dysfunction including deficient temperature regulation, chronic diarrhea, and ambiguous genitalia with micropenis and cryptorchidism.\textsuperscript{63,90} Early death is not uncommon.\textsuperscript{49} 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 glial white matter containing numerous heterotopic neurons, and complete agenesis of the corpus callosum without Probst bundles.\textsuperscript{88}

Mutations of the \textit{X-linked aristaless}-related homeobox gene (\textit{ARX}) (Mendelian Inheritance in Man #300382) were identified in individuals with \textit{X}-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia and in some female relatives.\textsuperscript{86} Females carrying abnormal \textit{ARX} usually have a normal cognitive level and can either have normal brain MRI or show partial or complete agenesis of the corpus callosum. However, mild mental retardation and epilepsy have been reported in rare female carriers.\textsuperscript{86} Mouse \textit{Arx} and human \textit{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.\textsuperscript{90,91} \textit{Arx}-deficient mice show deficient tangential migration and abnormal differentiation of interneurons containing GABAergic interneurons in the ganglionic eminence and neocortex. These characteristics recapitulate some of the clinical features of \textit{X}-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia in humans\textsuperscript{86} and might account for the severe neonatal epileptic encephalopathy with infantile spasms and suppression-burst EEG that is often observed in affected boys.

The mutations of the \textit{ARX} gene in patients with \textit{X}-linked lissencephaly with corpus callosum agenesis and ambiguous geni-
talia were primarily premature termination mutations (large deletions or frameshift, nonsense, or splice-site mutations). Missense mutations are less common and are essentially located in the homeobox domain.89 Patients carrying nonconservative missense mutations within the homeobox showed less severe X-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia, whereas conservative substitution in the homeodomain caused Proud syndrome (corpus callosum agenesis with abnormal genitalia). A nonconservative missense mutation near the C-terminal aristaless domain caused unusually severe X-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia with microcephaly and mild cerebellar hypoplasia. ARX mutations are also associated with milder phenotypes without malformations, including X-linked infantile spasms, Partington’s syndrome, and X-linked nonsyndromic mental retardation.92 Most patients with nonmalformation syndromes have polyalanine tract expansion mutations.92

MALFORMATIONS OWING TO ABNORMAL CORTICAL ORGANIZATION

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 clefts are most often found in the perisylvian area.93 Because the cortex surrounding the cleft of the fissure is polymicrogyric,94 schizencephaly is considered a disorder of cortical organization.7 However, a severe abnormality of neuronal precursor proliferation is also possible, especially when open lip clefts with absence of development of a large part of one cerebral hemisphere are considered. The walls of the clefts can be widely separated (Figure 8) or closely adjacent (Figure 9). Bilateral clefts are usually symmetric.94 Septo-optic dysplasia (agenesis of the septum pellucidum and optic nerve hypoplasia) is seen in up to one third of patients.90 Schizencephaly can 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 fibers during early gestation has been hypothesized. Schizencephaly is usually sporadic, but famil-
ial occurrence has been reported. Several sporadic patients and two siblings of both genders harboring germline mutations in the homeobox gene EMX2 have been described. However, the role of the EMX2 gene is still unclear, as are the possible patterns of inheritance and the practical usefulness that mutation detection in an individual with schizencephaly would carry in terms of genetic counseling. Clinical findings include focal seizures in most patients (about 80% of cases in one large review), usually beginning before age 3 years in bilateral cases. Bilateral clefts are associated with microcephaly, severe delay, and spastic quadriaparesis, whereas patients with unilateral schizencephaly most often have hemiparesis or can be brought to medical attention after seizure onset without having any other neurologic abnormality.

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 appearance. Cortical infolding and secondary, irregular thickening owing to packing of microgyri are visible on MRI (Figure 10), although mild forms are difficult to recognize on neuroimaging. Two histologic 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. In four-layered polymicrogyria, there is a layer of intracortical laminar necrosis with consequent impairment of late migration and postmigratory disruption of cortical organization. The two subtypes do not necessarily have a distinct origin because both can coexist in contiguous cortical areas.

The extent of polymicrogyria varies greatly, and there is a broad range of clinical manifestations, from severe encephalopathy with intractable epilepsy to individuals with only selective impairment of cognitive functions. Several syndromes featuring bilateral polymicrogyria have been described, including bilateral perisylvian polymicrogyria (Figure 11), bilateral parasagittal parieto-occipital polymicrogyria (Figure 12), bilateral frontal and frontoparietal (Figure 13) polymicrogyria, and unilateral perisylvian or multilobar polymicrogyria. 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. Affected individuals have continuous generalized spike-wave complexes during sleep and suffer from focal motor, atonic, and atypical absence seizures in the age range between 2 and 10 years. Epilepsy outcome is not
different from that seen in patients with cryptogenic electrical status epilepticus during sleep, that is, the seizures and EEG abnormalities disappear after a period of variable duration, but cognitive and behavioral disturbances, which are especially prominent in those children with longer electrical status epilepticus during sleep duration, often last.

Bilateral perisylvian polymicrogyria involves the gray matter bordering the sylvian fissure bilaterally. Both four-layered polymicrogyria and unlayered polymicrogyria have been observed. It is unclear whether these cases represent a spectrum of changes within a single malformation with the same etiology or different malformations, with different etiologies, with the same topography. 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. A locus for X-linked bilateral perisylvian polymicrogyria maps to chromosome Xq28 in some families. Bilateral perisylvian polymicrogyria has also been reported in some children with the chromosome 22q11.2 deletion and in children born from monochorionic diamniotic twin pregnancies that were complicated by twin-twin transfusion syndrome, confirming causal heterogeneity.

Affected patients have faciopharyngoglossomasticatory diplegia and dysarthria. Most have mental retardation and epilepsy. Those with more extensive damage can have spastic quadriplegia. Seizures usually begin between age 4 and 12 years and are poorly controlled in about 65% of patients. The most frequent seizure types are atypical absence seizures, tonic seizures, atonic drop attacks, and tonic-clonic seizures, often occurring as Lennox-Gastaut–like syndromes. A minority of patients (about 25%) have focal seizures only, predominantly involving the perioral or facial muscles. Infantile spasms have also been reported in a minority of patients. Patients with tonic or atonic seizures causing disabling drop attack can be amenable to anterior callosotomy, with interesting results. Lateralization of seemingly generalized seizures has been clearly documented after callosotomy in bilateral perisylvian polymicrogyria.

Bilateral frontal polymicrogyria was described in children with developmental delay, mild spastic quadriparesis, and epilepsy. Although most reported cases were sporadic, occurrence in offspring of consanguineous parents and in siblings was considered possibly suggestive of autosomal recessive inheritance. Indeed, frontoparietal polymicrogyria, a malformation extending only a few centimeters further back in the parietal lobes, was reported in several consanguineous and nonconsanguineous families, suggesting a recessive pattern of inheritance, and was initially mapped to chromosome 16q12.2-21 and subsequently associated with mutations of the G protein–coupled receptor gene 6 (GPR56). GPR56 belongs to the G protein–coupled receptor family, which is 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 harboring homozygous mutations, strongly suggests that Gpr56 regulates cortical patterning. The fact that the N-terminus domain that defines GPCR56 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. Epilepsy, seen in the majority of patients, was mainly accompanied by partial seizures and atypical absences and was of variable severity.
References


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