

Genetics of disorders of cortical development

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As MR imaging technology improves and becomes more widely used, the neuroradiologist is faced with an ever-increasing diversity of congenital brain malformations. Historically, many of these conditions were not regarded as genetic because parents of affected patients are not usually affected. Several recent developments, however, have shown that a large proportion of congenital malformations of the cortex are indeed caused by mutations in specific genes. The paradox of genetic causation in the absence of obvious genetic inheritance is resolved by consideration of the specific modes of genetic transmission of cerebral cortical malformations. For genes that act in dominant or X-linked fashion, in which a single mutant copy of a gene can cause a phenotype, the importance of de novo mutations, that are present in a child but not in the parents, is now understood. Moreover, there is an increasing recognition of subtle defects in cortical development, often with mild radiographic findings and mild clinical symptoms, which can be present in parents of more severely affected children. Finally, an increasing number of cortical malformations are ascribed to the action of recessive genes, for which both parents are asymptomatic carriers, but for which the family size is often too small to manifest

multiple affected offspring. This article provides an overview of major cerebral cortical malformations, focusing on the genetic mechanisms of their causation, and is intended to complement other articles in this volume that address the radiographic findings of congenital cortical malformations.

Classification

The classification of cortical malformations continues to evolve as knowledge of these disorders grows. Early schemes relied on pathologic and radiographic findings. More recent classifications have taken genetics into account [1]. Attempts to combine all aspects into a single classification system have not been completely successful. One part of the difficulty is the great heterogeneity of cortical malformations. A given gene defect can cause different phenotypic expressions. Likewise, a single phenotype may have multiple gene abnormalities associated with it. Such heterogeneity makes it difficult to give equal weight to all aspects of these disorders.

This article arranges cortical malformations according to the earliest embryologic stage in which the abnormality has its origin [1], although the stages of cortical development overlap in time and lack discrete boundaries. Moreover, some gene defects seem to exert influence in more than one developmental stage. Thus, the classification system presented here is not a final, definitive scheme and will undoubtedly be modified as knowledge of these conditions grows.

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Importance of embryology

Knowledge of embryology allows a perspective of where each malformation fits within the entire spectrum. Brain development begins in the third and fourth weeks of gestation with neurulation, the process of brain and spinal cord formation from the dorsal aspect of the embryo. In the fifth and sixth weeks, pattern formation, the process by which the brain takes shape, begins with prosencephalic development. In humans, cortical formation spans weeks 8 to 24 of gestation [2] and can be divided into stages of cell proliferation (when both neural and glial precursor cells are generated), neuronal migration (when cells travel from the proliferative zone to their designated destination), and cortical organization (when cell networks are determined) [1,3]. Myelination is the final step of brain development and continues well beyond birth [4]. These events occur in only rough sequence because different stages take place concurrently. Moreover, abnormalities of cortical development can result from impairments of more than one stage. It is nevertheless helpful to define stages for the purpose of classification. Abnormalities of cortical formation are the focus of this article.

Disorders of neural proliferation

Neural proliferation takes place between the second and fourth months of gestation. Radial glial cells, which play a critical role in neuronal migration [5] and which have recently been shown to represent the immediate progenitor cells for neurons [6–8], are also formed at this time. Neurons and glia have their origin in the ventricular and subventricular zones. In the earliest phases of neural proliferation, neuronal-glial stem cells predominantly divide to form further stem cells [9,10]. Later, stem cell division becomes asymmetric so that one daughter cell is postmitotic whereas the other remains a stem cell. Eventually, fewer and fewer stem cells are produced, and the proliferative region is progressively depleted [11,12]. Abnormal proliferation of neuronal progenitor cells may result in conditions characterized by too many or too few neurons.

Decreased proliferation

Congenital microcephaly

Congenital microcephaly is diagnosed when the head circumference is 3 or more SD below normal without evidence of in utero injury [13]. It is an extremely heterogeneous condition etiologically, be-

cause it can be caused by a host of environmental factors (eg, hypoxic-ischemic encephalopathy), or degenerative conditions. Now, however, a number of genetic causes of congenital microcephaly are recognized that present with a static picture and that reflect inadequate formation or survival of cerebral cortical neurons.

Most of the genetic forms of congenital microcephaly are inherited in recessive fashion, and in the past few years several genetic loci for recessive microcephaly have been mapped or cloned [14–23]. The most common genetic cause seems to be microcephaly 5 (MCPH5), caused by mutations in a gene called *ASPM* (abnormal spindle-microcephaly) [24]. Most patients with identified mutations are from Pakistan, and the prevalence of *ASPM* mutations in European and American populations is not known. These genetic forms of microcephaly usually present radiographically with a generalized simplification of the gyral pattern without gross gyral disruption. The extent to which the distinct genetic loci may have different radiographic patterns has not been investigated.

Microcephaly can also be associated with severely abnormal gyral patterns. Microcephaly with the most extensive gyral abnormalities is referred to as microlissencephaly [25,26], whereas milder gyral abnormalities are referred to as microcephaly with simplified gyral pattern [27,28]. These disorders have a much more severe clinical course than microcephaly alone. Seizures and global developmental delays are uniformly present, and the condition is often fatal in the neonatal period. The genetics of these conditions are not well established, but recessive genes are probably involved [27].

Disordered proliferation

Hemimegalencephaly

When unilateral enlargement of just one cerebral hemisphere exists, the condition is termed hemimegalencephaly. This condition has never been reported to be inherited, although its pathologic appearance suggests the abnormal action of genes involved in proliferation and differentiation [29,30]. Speculation about its cause focuses on somatic mutations of mitotic brain progenitor cells, in a fashion analogous to the de novo somatic mutations that cause spontaneous tumors in other tissues later in life. No firm evidence about mechanism is available, however. It may well result when a disturbance of cellular differentiation and proliferation interacts with the genetic expression of body symmetry [30]. In addition to increased size of the affected hemisphere, neuroimaging may reveal abnormal gyration, ventriculomeg-

aly, colpocephaly, displacement of the occipital lobe across the midline, and increased T2 signal of the white matter [29,30]. Histology reveals disorganized cortical lamination, dysmorphic neurons, and subcortical heterotopia [29–31]. Large, dysmorphic neurons, termed balloon neurons, are seen. The opposite hemisphere may be normal or have mild dysplasia and heterotopia [30]. All patients have epilepsy, which is often intractable, and most have mental retardation [30]. Hemispherectomy is often required for the management of intractable epilepsy [32].

Abnormal neuronal differentiation/maturation

Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) is a dominantly inherited, multisystem condition with a high rate of spontaneous mutations, so that about half of all affected patients have unaffected parents. It primarily affects the kidney, skin, and central nervous system where tumors, cysts, and hamartomas occur [33]. In the brain, the characteristic features include cortical hamartomas (cortical tubers), subependymal hamartomas (subependymal nodules), and giant cell astrocytomas [33]. Cortical tubers are firm and nodular, with a consistency resembling the potato tubers for which they are named. Microscopically, they demonstrate disorganized lamination within which are dysmorphic neurons possessing abnormal dendritic arborization and spine density [2]. Balloon neurons are also present. Beneath the cortex, nodular, periventricular collections of small cells exist and are termed subependymal nodules. In some instances, they transform into subependymal giant cell astrocytomas [34].

On MR imaging, cortical tubers appear as enlarged, atypically shaped gyri with abnormal signal intensity in the subcortical white matter. In neonates, subependymal nodules are hyperintense to white matter on T1-weighted imaging. In adults, they are isointense. Enhancement following the administration of intravenous contrast is variable [35].

Hamartomas of TSC likely arise by the two-hit tumor suppresser gene model first proposed by Knudson [36] for retinoblastoma. The afflicted individual inherits a germ-line TSC mutation from one parent. When this mutation is combined with the spontaneous loss of a second TSC allele, hamartomas or other tumors result. This model does not necessarily hold true for cortical tubers and subependymal nodules, because there is no evidence for loss of the second TSC allele in these lesions [37,38]. A second event may account for their appearance, given

their focal distribution, but the nature of that event remains uncertain.

Two genes have been cloned for TSC; both result in similar clinical and anatomic features. The *TSC1* gene located at chromosome 9q34 codes for a novel protein called hamartin, which indirectly links the cell membrane to the cytoskeleton [39,40]. *TSC2*, located at chromosome 16p13.3, encodes for the protein tuberlin, which may function in cellular signaling pathways [41]. Hamartin and tuberlin interact as part of a larger protein complex [39].

Focal cortical dysplasia

Focal cortical dysplasia (FCD), as described by Taylor et al [42], strongly resemble the cortical tubers of TSC. Macroscopically, the lesions display wider-than-normal gyri and blurring of the gray–white junction [43]. Microscopic findings include disordered cortical lamination with dysplastic, cytomegalic-appearing neurons and balloon cells. The underlying white matter is hypomyelinated and contains radially oriented balloon cells [43,44]. MR imaging shows the lesions to be slightly hyperintense on T2-weighted sequences. The hyperintense regions have a funnel-shaped appearance, with the base of the funnel oriented toward the pial surface, and the tip extending to the white matter. Because seizures resulting from FCD are commonly refractory to pharmacotherapy, surgical resection is often required and may even be curative.

The histology of FCD resembles tuberous sclerosis to such a large extent that they have been postulated to be the same entity, with FCD representing a forme fruste of TSC [45]. Although patients with FCD do not demonstrate the cutaneous and other systemic manifestations of TSC, FCD show an increase in *TSC1* polymorphisms and loss of heterozygosity at the *TSC1* locus [46]. The same alterations are associated with TSC, suggesting a common pathway in the development of these two disorders.

Schizencephaly

Schizencephaly is characterized by a cleft extending between the pial and lateral ventricular surfaces. The term was introduced in 1946 by Yakovlev and Waldsworth [47] to distinguish this malformative lesion from destructive disorders with a similar appearance (ie, porencephaly). Lining the cleft on both sides are abnormally small gyri, termed polymicrogyria. Schizencephaly is clinically heterogeneous [48]. It can be unilateral or bilateral; bilateral cases are more commonly associated with other cortical abnormalities. The clinical severity relates to the degree of structural involvement. Unilateral clefts commonly

present with hemiparesis and mild, if any, cognitive delay. Bilateral clefts, on the other hand, are associated with quadriplegia and significant cognitive impairment [48]. The severity of epilepsy is generally unrelated to the structural findings, however [49].

Possible causes are similarly heterogeneous. Environmental factors, such as fetal hypotension, exposure to organic solvents, and viral infections, may be causative [48]. Vascular anomalies have also been reported in association with schizencephaly [48]. Familial cases exist, indicating a genetic mechanism in some instances. In 1996, Brunelli et al [50] reported heterozygous mutations in the homeobox gene *EMX2* in seven sporadic cases. The same group later reported two brothers with the same *EMX2* deletion and different degrees of schizencephaly [51]. The authors postulate that although the gene mutation is causative, environmental factors may affect severity, and the utility of genetic testing in this condition is uncertain [52].

Disorders of neuronal migration

Migration takes place between the third and fifth months of gestation, during which time postmitotic neurons move from the ventricular and subventricular layers to their final sites within the cerebral cortex. Migration occurs in radial (perpendicular to the pial surface) and tangential (parallel to the pial surface) fashions [53]. Tangentially migrating neurons are more likely to become interneurons, whereas radially migrating neurons become projection neurons.

The radial glial cells seem to serve as a guide for radially migrating neurons [5], although nonradial forms of migration do not seem to depend upon radial glia. The earliest born neurons organize into a collection termed the preplate [54]. Later neuronal populations, known as cortical plate neurons, deposit in the preplate, dividing it into an outer marginal zone (just beneath the pial surface) and a deeper subplate layer [55]. Cortical plate neurons migrate in an inside-out fashion [56]. The first neurons to migrate occupy the deepest positions within the cortex, and those migrating later must squeeze past the earlier neurons to occupy a more superficial location facing the marginal zone [9]. A host of molecular determinants are necessary for the process to occur successfully.

Heterotopia

Heterotopia are collections of normal nerve cells in an abnormal location. It can be argued that all disorders of neuronal migration are heterotopia, but in practice the term refers only to conditions in which the ectopic neurons are located somewhere other than

cortex [57]. Unlike cortical dysplasia, the neurons within heterotopia usually appear normal and have normal MR imaging signal characteristics. Thus, on imaging, heterotopia are isointense with normal gray matter, lacking the abnormal signal intensity seen in dysplasia. Because of the arrest in migration, the cortex overlying heterotopia may be abnormally thin with shallow sulci [57].

Familial periventricular heterotopia. Familial periventricular heterotopia (PH)—also known as subependymal nodular heterotopia—are characterized by periventricular nodules of neurons resting beneath an otherwise normal-appearing cortex [58,59]. The nodules are rounded, irregular, and separated from each other by myelinated fibers. In PH, some neurons migrate fully to form a normal-appearing six-layer cortex, whereas others fail completely to migrate and remain in nodular collections within the subependymal region. The cortex functions surprisingly well, and most patients have normal intelligence [57,60]. Epilepsy, however, is common. It ranges from mild to severe and generally develops in the mid-teenage years [58]. Familial PH commonly displays X-linked dominant inheritance and is lethal in hemizygous male embryos [58]. At least half of affected patients have a *de novo* mutation not present in the parents [61]. In additional cases, a family history of the malformation (typically in the mother) is revealed only by MR imaging analysis, because one quarter or more of patients with the malformation have mild or absent seizures and few other signs or symptoms. PH most often results from a mutation of the filamin A (*FLNA*) gene on chromosome Xq28 [60]. *FLNA* encodes a large actin binding protein that aids in the structuring of actin networks at the leading edge of motile cells [62]. In doing so, *FLNA* is necessary for migration of neurons and other cell types including macrophages [63] and melanocytes [64]. It also plays a role in coagulation and vascular development; disruption of these functions probably accounts for male lethality [60].

In PH, only some of the neurons demonstrate a failure of migration; others go on to form a normal six-layered cortex. Originally the differing behavior was attributed to genetic mosaicism from random X-inactivation. Males with PH from *FLNA* mutations have been described [61], however, evidence that speaks strongly against X-inactivation as the basis for the divergent behavior of neurons in PH. The highly homologous protein, filamin B (*FLNB*), may help compensate for the loss of *FLNA* function and allow for proper neuronal migration of some neurons [65].

Autosomal recessive periventricular heterotopia. In a small minority of patients, PH displays autosomal recessive inheritance. Two pedigrees have been described in which the affected members did not demonstrate any association with *FLNA* or *FLNB* mutations, suggesting a distinct genetic mechanism in these families [66]. The gene for this autosomal recessive form of PH has recently been mapped and cloned, and encodes a guanosine triphosphate (GTP)ase exchange factor (*ARFGEF2*) that is involved in vesicle transport through the Golgi apparatus [67]. How the mechanism of action of the *ARFGEF2* protein might relate to the action of *FLNA*, or whether the two proteins have similar mechanisms, is not known. Additional genes exist for other forms of PH, and remain to be identified [68].

Lissencephaly

Lissencephaly means “smooth brain,” referring to a paucity of normal gyri and sulci. Agyria, also termed complete lissencephaly, describes a total absence of gyri, whereas pachygyria, or incomplete lissencephaly, is defined as a reduced number of abnormally flat and broad gyri. Lissencephaly is heterogeneous in its histology, etiology, radiographic appearance, and clinical features. It is traditionally divided into two pathologic subtypes: classic, or type I, and cobblestone, type II, lissencephaly. Radiographically, the cortex appears smooth in both types, but otherwise few similarities exist. Classic lissencephaly results from an arrest of neuronal migration, whereas cobblestone lissencephaly develops from overmigration. In either case, lissencephaly is generally associated with epilepsy and severe developmental delay.

Classic lissencephaly (agyria-pachygyria complex). Most patients with classic (type I) lissencephaly have a combination of both agyria and pachygyria. The clinical severity is largely related to the degree of structural abnormality, with greater gyral simplification resulting in greater clinical impairment. Radiographically, patients with agyria have a smooth brain surface with diminished white matter and shallow sylvian fissures [1,69]. In pachygyria, a reduced number of abnormally broad and flat gyri are seen [69]. Microscopically, areas of agyria demonstrate an outer, cell-sparse layer, then a thin neuronal layer, another cell-sparse zone, and then a thick layer of ectopic neurons, with the neurons arranged in no obvious relationship to the six layers that characterize the normal cortex [70]. By contrast, pachygyria displays better cortical organization, although the normal six layers are also frequently obscured.

LIS1 mutations and classic lissencephaly. Classic lissencephaly is most commonly caused by a disruption of the platelet-activating factor acetylhydrolase gene (*PFAH1B1*; also known as *LIS1*) located on chromosome 17p13 [71]. Virtually all patients have spontaneous, heterozygous deletions of *LIS1* that are not present in the parents, and the risk of having a second affected child is low. When a large deletion occurs, other congenital anomalies can result and together are termed the Miller-Dieker syndrome [70]. Because *LIS1* is an autosomal gene, each individual has two inherited copies, but a deletion of just one copy causes lissencephaly, indicating haploinsufficiency. That is, a 50% reduction in the *LIS1* protein is sufficient to account for the disorder. A homozygous deletion, on the other hand, is thought to be incompatible with life, as is the case in mice and *Drosophila* [72,73]. Thus, *LIS1* has widespread essential functions. Its localized effect on brain development in the heterozygous state indicates that neurons are more dependent on *LIS1* than other cell types. Consistent with this notion, *LIS1* is highly expressed by migrating neurons during brain development [74]. *LIS1* is also believed to interact with the microtubule motor cytoplasmic dynein [75–77]. In doing so, it may be involved in dendritic formation, axonal transport, and mitosis. A delay in mitosis and the resulting disruption in timing of neuronal proliferation may indirectly account for the disturbance in neuronal migration [78]. The precise cause of the human malformation is still not completely understood, however.

X-linked lissencephaly and subcortical band heterotopia. Another gene known to cause classical lissencephaly is doublecortin (*DCX*), located on the X chromosome [79,80]. In hemizygous males, the phenotype is nearly indistinguishable from *LIS1*. In heterozygous females, however, a disorder termed double cortex (DC), also known as subcortical band heterotopia, results [79]. As in other severe malformations, more than half of the patients with either X-linked lissencephaly or subcortical band heterotopia have de novo mutations not present in their parents [81]. In DC, the outer cortex displays normal six-layered architecture, but an inappropriate accumulation of neurons exists in the subcortical white matter. Random inactivation of the X chromosome probably accounts for this pattern, although this supposition is unproven. Half of the neurons express a normal copy of the doublecortin gene and undergo normal migration, whereas the other half express the mutant copy and remain arrested in the subcortical white matter. Males have only one X chromosome, so the mutation

affects all neurons. Hence, the more severe phenotype of classic lissencephaly occurs in males. Females with DC display mild to moderate mental retardation, and their epilepsy is generally less severe than in males with lissencephaly [82,83].

Like *LIS1*, *DCX* encodes a microtubule-associated protein [84]. It has been postulated that the two act on the same microtubule-based events in neuronal migration. After all, *LIS1* and *DCX* mutations result in nearly identical phenotypes, both genes code for microtubule-associated proteins, and *LIS1* and *DCX* proteins have potential interactions [85]. Yet, surprisingly, *LIS1* and *DCX* expression in humans has been reported to be strikingly disassociated [86], suggesting potentially separate roles in neuronal migration. *LIS1* is widely expressed in all migrating neurons and may be essential for cell motility in general. *DCX*, however, is absent in radially oriented neurons but present in tangential neurons [86]. Its role may therefore be specific to nonradial, radial-glia independent migration.

X-linked lissencephaly with abnormal genitalia. A second X-linked form of lissencephaly with abnormal genitalia (XLAG) has been described more recently and has several radiographic differences from that seen with *LIS1* or *DCX* mutations. XLAG is associated with a much thinner cortex than seen in classic lissencephaly and has associated malformations of the genitalia. Unlike those with *DCX* mutations, XLAG-carrier females are typically unaffected radiographically. XLAG is associated with mutations in the *ARX* gene, encoding a human homologue of the fly *aristal-less* gene [87,88]. Mutations in the *ARX* gene cause a striking range of phenotypes, including nonsyndromic mental retardation, severe seizures (West's syndrome), and finally lissencephaly with the most severe mutations [89–91]. The gene is expressed both in dividing and migrating cells, especially in nonmigrating cells, and so it seems to have functions in a number of stages of cortical development [88].

Autosomal recessive lissencephaly with cerebellar hypoplasia. Another form of lissencephaly has been analyzed recently and represents mutations in a gene called *RELN*, encoding a protein reelin [92]. This form of lissencephaly is rare and is quite distinctive radiographically because of the severely small cerebellum and hypoplasia of the brainstem and milder reduction of cortical gyri. Although Norman and Roberts [93] described a recessive form of lissencephaly many years ago, their original family did not show cerebellar hypoplasia and so represents a dis-

tinct form of lissencephaly not yet described at the genetic level.

Cobblestone (type II) lissencephaly. Whereas classic lissencephaly occurs following an arrest of neuronal migration, cobblestone lissencephaly develops from an overmigration of neurons beyond the pial surface and onto the overlying subarachnoid tissue. Cobblestone lissencephaly is often associated with congenital muscular dystrophy and eye abnormalities as is the case in Fukuyama congenital muscular dystrophy (FCMD), Walker-Warburg syndrome (WWS), and muscle-eye-brain disease (MEB). Other overlapping features include cerebellar dysplasia, hypomyelination, and hydrocephalus [94]. These disorders are believed to result from an impairment of glycosylation [95]. *O*-mannosylation is the specific type of glycosylation implicated. *O*-mannosylation is specific to brain, nerve, and skeletal muscle, explaining the distribution of involved tissues in these disorders [96].

Of all three disorders, WWS has the most severe phenotype; it is often fatal in the first year of life [97]. In addition to cobblestone lissencephaly, patients with WWS sometimes display agenesis of the corpus callosum, cerebellar hypoplasia, hydrocephalus, and encephalocele. Neuroimaging reveals a thickened cortex with few, abnormally shallow sulci. The gray–white matter junction is irregular because of disorganized collections of neurons misplaced in the white matter. Hypomyelination is common [94]. Genetically, WWS is recessively inherited. The syndrome results from mutations in the *O*-mannosyltransferase 1 (*POMT1*) gene [98], implicating a failure of glycosylation as the primary defect. Consistent with this theory, patients with WWS from *POMT1* mutations demonstrate an absence of glycosylation of alpha-dystroglycan [98].

MEB is also an autosomal recessive condition and is most prevalent in Finland. The clinical severity is intermediate to WWS and FCMD [99], as is the radiographic appearance [94]. MEB results from loss of function mutations in the gene encoding protein *O*-linked mannosyltransferase 1 (*POMGnT1*) [100]. A genotype–phenotype correlation exists in MEB patients. Mutations close to the 5' terminus of the *POMGnT1* gene result in a severe clinical picture, and mutations at the 3' terminus lead to milder impairments [101].

FCMD is, in general, the mildest of the three disorders. It presents with hypotonia and global developmental delays. Seizures develop in the first year of life in half of patients [102]. FCMD is associated with mutations of the gene fukutin on chromosome 9q31 [103]. Although the exact function of fukutin is

unknown, its structure predicts it to be an enzyme involved in the modification of surface glycoproteins or glycolipids. FCMD is postulated to have a pathophysiology similar to that of MEB in which defects of *O*-mannosylation compromise laminin binding [96]. FCMD is seen primarily in Japan, where 94% of the affected individuals share a common haplotype, indicating a single founder in the Japanese population [103]. Patients who are homozygous for the founder mutation have a higher residual activity of fukutin and a milder phenotype than patients with a spontaneous point mutation on the second allele (compound heterozygotes) [104]. It can be difficult to distinguish severely affected FCMD cases from WWS patients. Recently, two Turkish individuals with mutations of fukutin were reported as displaying a WWS phenotype [105]. Such overlap implies a shared pathway in the pathophysiology of these disorders. These several glycosyltransferases are thought to all converge on a common target, α -dystroglycan, which is an essential link between cell membranes and the extracellular matrix [106,107].

Symmetric polymicrogyria

Polymicrogyria is thought to develop at the latest stages of neuronal migration or the earliest phases of cortical organization [1]. It often results from external causes such as intrauterine cytomegalovirus infection or placental perfusion failure. Genetic causes do exist, however, and tend to result in focal but symmetric lesions. Syndromes affecting every conceivable region—fronto-parietal, perisylvian, parieto-occipital—have been observed. Epilepsy and cognitive delays are common among all of the syndromes; additional symptoms depend upon the specific regions affected.

Bilateral frontoparietal polymicrogyria. Bilateral frontoparietal polymicrogyria is characterized by bilateral, symmetric polymicrogyria in the frontoparietal regions [108]. There is a decreasing gradient of severity from the anterior to posterior direction. The white matter is thin with areas of T2 prolongation, the ventricles are enlarged, and the pons and cerebellar vermis are abnormally small [108]. The clinical manifestations are consistent: motor abnormalities, seizures, and global developmental delay are universal [108]. Cerebellar abnormalities and disconjugate gaze are also common. The disorder has been mapped to chromosome 16q12.2–21 [108,109], and the responsible gene has recently been identified as *GPR56*, which encodes a G-protein–coupled receptor [110]. Patients with bilateral frontoparietal polymicrogyria are characteristically from the Middle East or from the

Indian subcontinent, although cases from Canada and the United States have been observed [108].

Bilateral perisylvian polymicrogyria. Bilateral perisylvian polymicrogyria results in a clinical syndrome manifested by mild mental retardation, epilepsy, and pseudobulbar palsy [111]. The pseudobulbar palsy specifically affects expressive speech and feeding. Bilateral perisylvian polymicrogyria is often a sporadic condition. It has been described in association with unrelated disorders including neurofibromatosis type I [112] and Kabuki syndrome [113]. Bilateral perisylvian polymicrogyria is therefore likely to be heterogeneous genetically. In some pedigrees, bilateral perisylvian polymicrogyria follows an X-linked inheritance pattern, and linkage analysis places the critical region at Xq28 [114].

Summary

The list of genetically characterized malformations of the cerebral cortex continues to grow, and the rate of growth is accelerating. There are still dozens of syndromes that have not yet received their definitive description, much less their genetic characterization. The absence of a family history should by no means rule out a genetic condition, because many genetic conditions are recessively inherited or caused by *de novo* mutations. The radiographic features are an increasingly specific and sensitive guide to genetic (or nongenetic) causation and are important in directing the genetic workup. As more is learned about genetic causes of cortical malformations, this genetic information will be increasingly integrated into the interpretation of MR imaging to increase its specificity even further.

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