CHAPTER

115

Genetic Disorders of Cerebral Cortical Development

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115.1 INTRODUCTION

The widespread clinical use of MRI, with its ability to image the human brain noninvasively, has revolutionized our understanding of cerebral cortical malformations. Although some dramatic cortical malformations can be associated with remarkably preserved intellect, most brain malformations cause severe neurological disability. Genetic disorders of cortical development include sporadic noninherited anomalies, as well as a growing variety of malformations with distinct inheritance patterns. Consequently, accurate diagnosis and genetic counseling requires precise definition of the anatomical abnormalities and the clinical spectrum of each disorder. Since malformations of the cerebral cortex have their origins during the dynamic process of cortical development, understanding normal cortical development is essential when considering these disorders. Therefore, the process of normal development of the human cerebral cortex will be reviewed briefly before discussing individual cortical malformations.

The neurons of the cerebral cortex are formed in a pseudostratified columnar neuroepithelium of the ventricular zone and then migrate over considerable distances to reach their final destination in the cortex. Neural progenitor cells in the ventricular zone are called radial glia cells (*1*). They give rise to postmitotic neurons, which migrate toward the surface, and also to a secondary population of progenitor cells in the subventricular zone (the region immediately superficial to the ventricular zone) (*2*). The subventricular zone contains two major types of progenitors. Basal progenitors appear to be short-lived intermediate progenitors that produce individual cell types such as neuron or glia (*2–5*). In addition, a recently described population of multipotential progenitors with radial glia-like morphology in the outer subventricular zone is especially common in the brains of humans and other mammals with a large cerebral cortex (*6–8*).

The first group of postmitotic neurons produces a pioneer layer called the primordial plexiform layer (*9*,*10*). This layer, also called the "preplate" is later split into an outer layer ("marginal zone") and a deeper layer ("subplate") by the later-arriving neurons that form the cortical plate. Neurons add to the cortical plate in an inside out manner, so that newer-arriving neurons always migrate past the older cortical plate neurons until they arrest next to the marginal zone (*11*,*12*). The marginal zone, which contains specialized neurons called Cajal-Retzius cells, seems to be instrumental in establishing the inside out laminar gradient of the cortical plate. In the human cortex, postmitotic neurons start to migrate out of the ventricular zone between the sixth and seventh week of gestation to form the primordial plexiform layer (*10*,*13*). Migration of neurons appears to peak between the 11th and 15th week of gestation (*11*). Although it is not entirely clear when migration is finally completed in the cerebral cortex, the majority of neurons have entered the cortex by around the 24th week of gestation (*10*,*14*).

The migration of cortical plate neurons is guided by long radially aligned fibers of radial glial cells (*12*,*15*,*16*). The outermost processes of these radial glial cells form the outer limiting membrane of the brain, consisting of glial endfeet apposed to a basement membrane contributed both by neural and extra-central nervous system (CNS) cells [reviewed in (*17*)]. Nonradial (tangential) neuronal migration is also common in the developing cortex (*18*), with a large fraction of cerebral cortical neurons, particularly inhibitory interneurons, originating outside of the cortex itself, in other brain regions that give rise to the basal ganglia (*19–21*). A vast diversity of molecules has been implicated in the development of the cortex through animal studies but will be reviewed here only if they specifically relate to known human genetic disorders.

Although a standard and universally applied classification scheme for malformations of cortical development is yet to be developed, a system proposed by Barkovich et al. (*22*,*23*) serves as a useful framework (Table 115-1). The Barkovich et al. scheme is primarily organized according to a triad of embryology, genetics, and neuroimaging. Our presentation of cortical disorders will generally follow this outline.

115.2 MALFORMATIONS DUE TO ABNORMAL NEURONAL AND GLIAL PROLIFERATION OR APOPTOSIS

115.2.1 Microcephaly: An Overview

Microcephaly is a condition in which the cranial vault, defined by the occipitofrontal head circumference (OFC), is significantly smaller than expected for an individual's age and sex (>2 standard deviations smaller than the mean; or more conservatively, >3 standard deviations) (*24*,*25*). The etiology of microcephaly is extremely diverse, posing significant challenges to clinicians dealing with this condition, but can be broadly divided into environmental and genetic causes (*26*). Common environmental causes include congenital infection, intrauterine exposure to teratogenic agents, and hypoxic-ischemic injury. The clinical history usually provides important diagnostic clues in these cases. On the other hand, genetic causes of microcephaly are also quite diverse. Inherited metabolic disorders usually cause postnatal onset of microcephaly (acquired microcephaly) and are not discussed here.

Genetic causes of microcephaly that are associated with the presence of microcephaly at birth (congenital microcephaly) usually represent developmental malformations of the cerebral cortex. For example, microcephaly is frequently seen in association with a variety of chromosomal abnormalities and other well-defined genetic syndromes (e.g. Smith-Lemli-Opitz syndrome; OMIM 270400) that are discussed elsewhere in this book. In these cases, the characteristic patterns of involvement of other organ systems and/or the presence of specific dysmorphic features often help make the diagnosis. Other well-characterized CNS disorders such as neuronal migration disorders (e.g. lissencephaly) can be associated with microcephaly without other organ involvement, and these conditions are described later in the chapter. Finally, there are an increasing number of syndromes and genetic loci (e.g. microcephaly vera) in which the CNS is typically the only affected organ system and in which the brain is characteristically quite small. These disorders are discussed below.

TABLE 115-1 Classification of Cortical Malformations

I. Malformations due to abnormal neuronal and glial proliferation or apoptosis
A. Decrease proliferation/increased apoptosis (microcephaly)
1. Microcephaly with normal or mildly simplified gyri
a. Microcephaly vera (primary autosomal recessive microcephaly)
b. Microcephaly, seizures and developmental delay (early infantile epileptic encephalopathy 10)
c. Microcephaly with proportionate short stature
d. Others
2. Microlissencephaly (severe microcephaly with significant simplification of gyri)
3. Microcephaly with other brain malformations (e.g. polymicrogyria, pontocerebellar hypoplasia)
B. Increased proliferation/decreased apoptosis (megalencephaly)
C. Abnormal proliferation and differentiation (nonneoplastic)
1. Cortical tubers of tuberous sclerosis
2. Focal cortical dysplasia
3. Hemimegalencephaly
II. Malformations due to abnormal neuronal migration
A. Classical lissencephaly/subcortical band heterotopia
1. LIS1-associated lissencephaly
2. X-linked lissencephaly 1
3. X-linked lissencephaly 2
4. TUBA1A-associated lissencephaly
B. Cobblestone dysplasia
C. Gray matter heterotopia
1. X-linked periventricular heterotopia
2. Autosomal recessive periventricular heterotopia with microcephaly
3. Heterotopia due to chromosomal aberration
III. Malformations due to abnormal cortical organization (including later stages of neuronal migration)
A. Polymicrogyria
1. Bilateral frontoparietal polymicrogyria
2. Bilateral perisylvian polymicrogyria
3. Bilateral occipital polymicrogyria
4. Bilateral generalized polymicrogyria
5. Other localized polymicrogyria syndromes
6. Tubulin-associated polymicrogyria
7. Polymicrogyria due to chromosomal aberration
B. Schizencephaly
IV. Malformations of cortical development, not otherwise classified
A. Malformations secondary to inborn errors of metabolism
B. Others

Modified from (*22*,*23*).

115.2.2 Microcephaly Vera

This term, meaning "true" microcephaly, was coined by Giacomini in 1885 to denote a condition in which no gross pathological abnormality other than the small size of the brain was observed (*27*). Clinically, this term has been used to describe a group of patients characterized by the presence of microcephaly at birth, relatively normal early motor milestones, and intellectual disability of variable severity. Microcephaly is usually profound, ranging between –4 and –12 standard deviations below the mean for the age (*28*,*29*). Usually there are few dysmorphic features other than those that arise as a consequence of the microcephaly, including a narrow sloping forehead and relative prominence of ears. Seizures are relatively uncommon in this group of patients, although reported in some cases (*30*). When early-onset seizures are a prominent feature but the rest of clinical characteristics resemble microcephaly vera, patients may fall into the category of the recently characterized syndrome of microcephaly, seizures, and developmental delay (see below).

115.2.2.1 Genetics and Biology. Microcephaly vera is inherited as an autosomal recessive trait, and it is genetically highly heterogeneous. To date, seven genes in seven loci (termed MCPH1 through 7) have been identified to be associated with microcephaly vera: *MCPH1* (also known as *microcephalin*; the MCPH1 locus; OMIM 251200) (*31*), *WDR62* (MCPH2; OMIM 604317) (*32–34*), *CDK5RAP2* (MCPH3; OMIM 604804) (*35*), *CEP152* (MCPH4; OMIM 604321) (*36*), *ASPM* (MCPH5; OMIM 608716) (*37*), *CENPJ* (MCPH6; OMIM 608393) (*35*) and *STIL* (MCPH7; OMIM 612703) (*38*). Among these genes, *ASPM* mutations appear to be the most common and may account for approximately 40% of patients who fit the clinical description of microcephaly vera (*39*,*40*).

Upon brain MRI, patients with microcephaly vera typically show a normal or mildly simplified gyral pattern. Cortical thickness appears normal. In patients with *ASPM* mutations, associated abnormalities such as agenesis of corpus callosum, enlarged lateral ventricles (particularly of the occipital horn), and focal cortical malformations (e.g. unilateral polymicrogyria or focal cortical dysplasia) are sometimes seen (*41*). *WDR62* mutations are associated with the more frequent presence of associated structural abnormalities, which include severe simplification of gyri, polymicrogyria hypoplasia or partial agenesis of the corpus callosum and schizencephaly (*32–34*). Missense *WDR62* mutations appear to be associated with less severe structural abnormalities compared to truncating mutations (*33*).

The proteins encoded by the genes associated with microcephaly vera localize, at least in part, to the mitotic centrosomes and are involved in the regulation of cell cycle and cell division during early cortical development (*28*). Thus these proteins are thought to regulate proliferation of neural progenitor cells in the developing cerebral cortex. Although the exact mechanisms by which these proteins regulate cell cycle and cell division are not entirely clear, ASPM has been shown to maintain symmetrical cell division (in which neural progenitors generate two progenitors as daughter cells, as opposed to generating one progenitor and one postmitotic neuron) (*42*). This function likely prevents premature depletion of neural progenitors. MCPH1 contains three BRCT (BRCA1 C-terminal) domains. Many proteins with this domain are known to function in DNA repair, and MCPH1 has also been implicated in DNA damage response (*43*). In addition, it is implicated in chromosome condensation during mitosis (*44*) and chromatin remodeling (*45*).

Patients with congenital microcephaly who also have intractable seizures starting during infancy have been found to have recessive mutations in the DNA repair protein gene *PNKP* (*46*). This entity is variably called microcephaly, seizures, and developmental delay or early infantile epileptic encephalopathy 10 (OMIM 613402). These patients typically show head circumference of –2 to –3 SD at birth and –4 to –7 SD during childhood and have severe intellectual disability. However, milder mutations lead to milder microcephaly (–2 to –3 SD below the mean during childhood) and less severe seizures and intellectual disability. Unlike other disorders that affect DNA repair (e.g. ataxia telangiectasia), microcephaly due to mutations in *PNKP* has not been associated with immunodeficiency or cancer, although no long-term follow-up is available for patients with *PNKP* mutations.

Patients with microcephaly vera have severe microcephaly, but their linear growth is much less affected. On the other hand, there are patients with severe congenital microcephaly with proportionate growth retardation. Clinical entities associated with this type of presentation include Seckel syndrome (OMIM 210600 for the *SCKL1* locus) and microcephalic osteodysplastic primordial dwarfism types I (MOPD I; OMIM 210710) and II (MOPD II; OMIM 210720). Some patients with Seckel syndrome have been found to have recessive mutations in *ATR* (*47*), which is closely related functionally to *ATM*, the gene mutated in ataxia telangiectasia, and is also involved in DNA damage response (*48*). Recessive mutations in one of the genes associated with microcephaly vera, *CEP152*, have also been found in patients with a diagnosis of Seckel syndrome (*49*), suggesting overlap between these two conditions. MOPD II has been associated with recessive mutations in *PCNT2*, whose protein product localizes to centrosome (*50*,*51*) but may also be involved in DNA damage response like ATR and MCPH1 (*50*). Thus these microcephaly syndromes with short stature and microcephaly vera may represent defects in overlapping biological pathways.

An autosomal dominant form of microcephaly (OMIM 156580) has been described and is perhaps

relatively common among individuals with mild (–2 to –3 SD) microcephaly, but little is known about its cause. This form of microcephaly is often associated with normal intelligence and may not come to clinicians' attention very often (*52*). The assessment of recurrence risk of microcephaly is therefore often challenging because of the heterogeneous nature of this condition. Unless the mode of inheritance is evident from family history, examination and laboratory investigations, accurate assessment may be difficult. In one population-based study in British Columbia, Canada, the recurrence risk of intellectual disability in the siblings of microcephalic individuals was estimated to be 5.9%, one-third of whom also had microcephaly (*53*). Another study estimated the recurrence risk of microcephaly in siblings of microcephalic individuals to be 19% (*54*), more suggestive of an autosomal recessive trait. This large difference may be due to differences in the percentage of autosomal recessive forms of microcephaly in each population studied.

In patients with microcephaly vera, the gyral pattern is relatively well preserved despite the often strikingly small size of the brain (Figure 115-1). Pathological studies of the brain are few, but they thus far reveal no microscopic abnormality in cortical laminar formation (*55*,*56*). In some cases, a reduced number of neurons in cortical layers II and III, which are superficial layers (*57*), or neuronal heterotopias (*55*) have been observed. Although a decreased number of neurons in the cerebral cortex is considered to be primarily responsible for the small size of the brain in microcephaly vera, there are many potential ways in which the number of cortical neurons can be subnormal. For example, decreased proliferation of neuronal progenitors, decreased production of mature neurons by each neuronal progenitor, or excessive cell death of neuronal progenitors or of mature neurons all lead to decreased numbers of neurons in animal models (*58*,*59*).

115.2.3 Microlissencephaly

It has been long known that some patients with congenital microcephaly present with more severe neurological signs, such as spasticity, severe developmental delay, and seizures. Some of those patients have striking simplification of cortical gyral pattern (more significant than what is seen in patients with microcephaly vera), and the term microlissencephaly (microcephaly + lissencephaly) may be applied to those cases (*60–62*). This is clearly a highly heterogeneous group. Survival varies significantly, with some patients dying within days or weeks (*63*) but others living for years. Associated neuroimaging findings may include pontocerebellar hypoplasia, enlarged extra-axial spaces, and polymicrogyria (*64*). This clinical and radiological variability may reflect their distinct pathogeneses.

115.2.3.1 Genetics and Biology. Recently, recessive mutations in the *NDE1* gene were identified in patients with severe congenital microcephaly, severe simplification of gyral pattern, and the variable presence of spasticity and seizures (*65*,*66*). The homolog of NDE1 in *Aspergillus nidulans*, NudE, is an essential regulator of nuclear migration pathway (thus the name Nuclear distribution E) and interacts with the homologs of LIS1 (whose mutations are associated with classical lissencephaly discussed below) (*67*). This interaction is also preserved in mammals (*58*,*68*,*69*). In addition, similar to other genes associated with microcephaly vera, NDE1 localizes to the mitotic centrosome, and its defects lead to failure in mitotic progression (*65*,*66*). Thus, the clinical characteristics of severe microcephaly associated with lissencephaly may be explained by the essential roles of NDE1 in both neurogenesis and neuronal migration. The genetic basis of other types of microlissencephaly has not been elucidated.

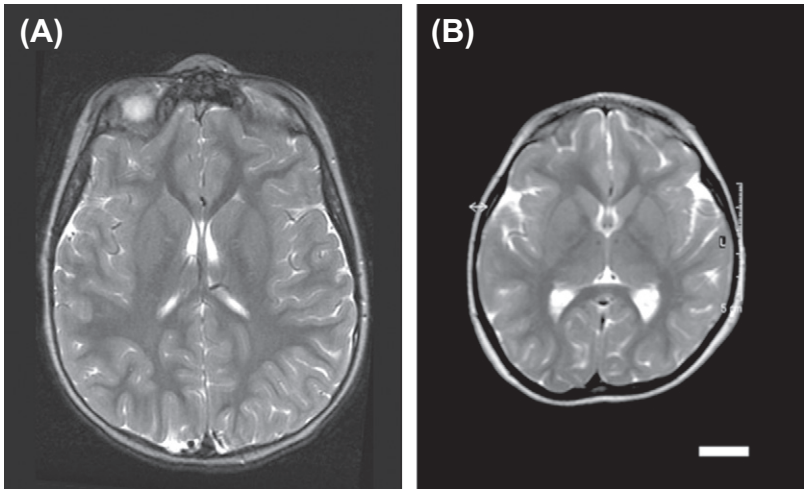

FIGURE 115-1 T2-weighted axial MRI images of a normal 4-year-old girl (A) and a 3-year-old girl with microcephaly vera (B) are shown. The gyral pattern is mildly simplified in the patient, but there are no other structural abnormalities, except for the striking smallness of the brain. The patient was found to have a mutation of the *ASPM* gene. Scale bar = 2 cm.

115.2.4 Other Microcephaly Syndromes

Several other novel microcephaly syndromes have emerged in recent years. Intellectual disability and variable postnatal microcephaly (ranging from normal to almost –6 SD below mean; MRT13; OMIM 613192) has been associated with mutations in *TRAPPC9* (70–72). Brain MRI of these patients may reveal paucity and signal abnormalities of the cerebral white matter (70–72). The *CASK* gene on the X chromosome was found to be mutated in patients with congenital or postnatal microcephaly with disproportionate brainstem and cerebellar hypoplasia (OMIM 300749) (73).

115.2.5 Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC; OMIM 191100 for TSC1 and 613254 for TSC2) is an autosomal dominant multiorgan disorder that commonly affects the brain, eyes, skin, kidneys and heart. TSC is discussed in this section as its fundamental defects include cell proliferation, fate determination and differentiation. Neurological manifestations, which are usually the major clinical problems, include epilepsy, intellectual disability and autistic symptoms. In the brain, the characteristic lesions of TSC are cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas (SEGAs). Cortical tubers are circumscribed areas of dysplastic cortex, which appear pale and have firmer consistency compared to the normal cortex (74). Within the tubers, the normal laminar structure is lost and enlarged dysmorphic neurons as well as "giant cells" (or "balloon cells") with abundant eosinophilic cytoplasm are seen. These giant cells variably express neuronal and glial markers (75). In TSC, subependymal nodules project into the third and lateral ventricles as smooth firm nodules, forming classic "candle gutterings" (74). They may continue to grow and form SEGAs, but the molecular mechanisms of this transformation remain to be understood. Many of the histological features that are observed in cortical tubers are also seen in subependymal nodules and SEGAs, but the cellular packing density of these latter lesions is much higher than that of cortical tubers.

115.2.5.1 Genetics and Biology. TSC is caused by mutations in one of the two genes, *TSC1* and *TSC2*. In *de novo* cases, *TSC2* mutations have been found 2–10 times more often than *TSC1* mutations (76–81). However, about half of the familial cases are due to mutations in *TSC1* and the rest are due to mutations in *TSC2* (81,82). *TSC2* mutations are associated with a higher frequency of cystlike tubers, which may predispose to a more aggressive seizure phenotype (83). The *TSC2* gene in chromosome 16p13 encodes a protein called tuberin, which encodes a GTPase activating protein (GAP)-related domain (84). Tuberin has been shown to have GAP activity for Rap1 and Rab5 (85,86). The *TSC1* gene in chromosome 9q34 encodes a protein named hamartin (87). Tuberin and hamartin interact directly (88–90) and act as critical negative regulators of the mTOR (mammalian target of rapamycin) signaling pathway, an important pathway regulating cell growth in response to growth factors and other metabolic stimuli (91–93). Thus TSC lesions show abnormal mTOR activation, with enlarged and dysplastic-appearing cells.

The focal nature of TSC lesions appears to be explained by the "two-hit" hypothesis, originally developed by Knudson for the retinoblastoma gene (94). In the "two-hit" model, all somatic cells harbor a mutation in one allele, and a subsequent random "second hit" or spontaneous mutation in the other "healthy" allele is required for a dividing cell and the daughter cell of that cell to develop an abnormal phenotype. This hypothesis is supported by the fact that loss of heterozygosity (which indicates that the second hit has occurred) for *TSC1* or *TSC2* locus has been detected in some TSC lesions (95,96). In CNS lesions, loss of heterozygosity has been demonstrated to occur rarely if at all (97,98); whether this reflects a pathogenesis of CNS lesions different from other TSC lesions is unclear.

The central involvement of the mTOR pathway in the pathogenesis of TSC has led to the hypothesis that some manifestations of TSC may be amenable to treatment with rapamycin and its derivatives (99–102). The role of rapamycin vs neurosurgical intervention for the treatment of SEGAs is still to be determined at the time of the writing of this chapter (103), and clinical trials to evaluate the effects of rapamycin on neurocognitive outcomes in children with TSC are still in progress. TSC is an exemplar of a neurodevelopmental condition with potential disease-specific treatments that may follow from the study of the genetics of the disorder.

115.2.6 Focal Cortical Dysplasia

Focal cortical dysplasias (FCDs; OMIM 607341) are dysplastic zones of cortex, usually occurring as solitary lesions that interrupt the otherwise morphologically normal cortex. FCDs share some radiographic and histological similarities with the cortical tubers of TSC (104–106). Histologically, FCDs contain large bizarre neurons in all but the first cortical molecular layer, with a loss of cortical lamination. Grotesque, glia-like cells are present in the depth of the affected cortical region and in the underlying demyelinated white matter (105). "Balloon cells" with glassy eosinophilic cytoplasm and pleomorphic eccentric nuclei have been demonstrated in cases of FCD (105) and were found to express neuronal markers, glial markers, or both (107,108). FCD is a well-known cause of intractable epilepsy (109,110), but it is sometimes not identified in the initial MRI scan unless there is a high degree of suspicion for a focal abnormality at a specific location; appropriate signal sequences and reconstructions may need to be performed to optimize detection of small or relatively subtle FCD.

The most common MRI picture of FCD takes the form of a thickened bumpy cortex with shallow and wide sulci. Deep infoldings of thickened cortex may also be found (*104*).

The neuropathological findings of FCD, which are the basis of the classification of FCD into subtypes (*110*), have led to the hypothesis that FCDs may represent focal somatic mutations that have occurred early in cortical development, perhaps in the *TSC* genes or in related genes, but this has not been definitively demonstrated. The histological features of FCD are strikingly similar to that of TSC, and it has been debated whether sporadic FCD, in the absence of the other stigmata of TSC, represents a "forme fruste" of TS (*111*). Studies have shown different patterns of gene expression in these two disorders, and this may suggest distinct pathogenetic mechanisms at work (*112*,*113*). On the other hand, loss of heterozygosity at the *TSC1* locus has been identified in some of microdissected tissue samples of FCD, possibly suggesting a pathogenetic relationship (*114*,*115*).

FCD usually occurs in a sporadic, noninherited form. A pedigree was reported several years ago with apparent familial cortical malformations including FCD among other malformations; on careful inspection images from an affected individual with FCD appear more typical of asymmetric perisylvian polymicrogyria than the typical FCD (*116*). More recently, there has been one demonstration of a genetic etiology for focal cortical dysplasia in an Amish pedigree with an autosomal recessive mutation in the gene *CNTNAP2*; the affected individuals had medically intractable focal epilepsy, intellectual disability, and aggressive behavior (*117*). *CNTNAP2* has also been reported to be associated with autism (*118–121*) and Pitt-Hopkins-like syndrome 1 (OMIM 610042) (*122*).

115.2.7 Hemimegalencephaly

Hemimegalencephaly is characterized by unilateral enlargement of only one cerebral hemisphere. The entire cerebral hemisphere may be enlarged, but sometimes only half or part of the affected hemisphere is involved. The enlarged hemisphere usually shows gyral abnormalities in the form of agyria/pachygyria or polymicrogyria, and the lateral ventricle on the abnormal side is often enlarged (*123*). Boundaries of gray and white matter may be blurred, and gray matter heterotopia may be found. Microscopically, cortical laminar disorganization, neuronal cytomegaly, and heterotopic neurons in the white matter are seen (*124*,*125*). The diagnostic criteria for hemimegalencephaly are not precise, so the term is often applied to virtually any cortical malformation that involves most of a single hemisphere.

A typical clinical presentation includes contralateral hemiparesis, epilepsy, and intellectual disability (*123*). Seizures often start during the first days of life and are typically intractable to medical management. In fact, early resistance to antiepileptic drugs is common (*126*). Partial seizures with or without secondary generalization and infantile spasms are common (*127*,*128*). Hemispherectomy can be an effective treatment for seizure control (*126*). Cognitive development may vary widely. Patients with normal intellectual development have been reported (*129*), but this is uncommon.

Hemimegalencephaly can be seen as an isolated malformation or in association with various neurocutaneous syndromes such as hypomelanosis of Ito (OMIM 300337) (*130*,*131*), Shimmelpenning-Feuerstein-Mims syndrome (also known as linear sebaceous nevus syndrome or epidermal nevus syndrome; OMIM163200) (*132*,*133*), Proteus syndrome (OMIM 176920) (*134*), and Klippel-Trénaunay-Weber syndrome (OMIM 149000) (*135*). In addition, rare association with neurofibromatosis type I (OMIM 162200) (*136*) and TSC (OMIM 19100 and 613254) (*137*) have been reported. Thus, a careful skin examination is mandatory in patients with this condition. Hemimegalencephaly is typically encountered as a sporadic, noninherited condition. Therefore, the risk of recurrence is considered small when there is no association with a known inherited syndrome.

Histological characteristics, such as neuronal cytomegaly and heterotopic neurons, closely resemble TSC and FCD. In some cases, "balloon cells" similar to those seen in TSC and FCD are also observed. In contrast, a comparison between "balloon cells" seen in hemimegalencephaly vs TSC has shown different immunohistochemical and ultrastructural characteristics of the abnormal neurons in each condition (*138*). It is conceivable that somatic mosaicism may play a role in the pathogenesis of hemimegalencephaly, but definitive evidence is lacking.

115.3 MALFORMATIONS DUE TO ABNORMAL NEURONAL MIGRATION

115.3.1 Classical Lissencephaly: An Overview

Lissencephaly represents a smooth brain with a lack or severe paucity of normal gyri. Classical (or Type I) lissencephaly is characterized by a severely thickened cerebral cortex with three or four abnormal layers instead of the normal six cortical layers. On the other hand, "cobblestone" (or Type II) lissencephaly is a completely different entity histologically (see Section 115.3.7). Several clinical entities are associated with classical lissencephaly, including isolated lissencephaly sequence (ILS), Miller-Dieker syndrome (MDS; OMIM 247200), X-linked lissencephaly 1 (OMIM 300067), and X-linked lissencephaly 2 (OMIM300215).

115.3.2 Isolated Lissencephaly Sequence and the Miller-Dieker Syndrome

The most common cause of classical lissencephaly is a mutation of an autosomal gene on chromosome 17p13

known as *LIS1*. Deletion or mutation in the *LIS1* gene is the cause of lissencephaly both in MDS and in ILS (*139*). Additional clinical findings in MDS include an abnormal facies with microcephaly, bitemporal hollowing with narrowing at the temples, tall and prominent forehead with vertical furrowing, hypertelorism with upward slanting palpebral fissures and ptosis, short nose with upturned nares, low-set ears with minor flattening of the helices, prominent philtrum with thin vermilion border of the upper lip, and small mandible (*140–142*). Digital abnormalities, such as syndactyly, congenital heart disease, and other visceral abnormalities may be seen in patients with MDS (*142–144*). Almost all children with classical lissencephaly have profound developmental delay and intellectual disability; many of them die during infancy or childhood. The majority of the patients have seizures, typically starting during the first 6 months of life (*143*,*145*).

On imaging studies, the cerebral hemispheres show agyria (lack of gyri) or pachygyria (broadening of gyri), and often these two features coexist. The frontal and temporal opercula (the parts of the brain that cover insular cortices) are not developed, leading to a characteristic "figure-eight" shape appearance of the brain on axial images and bitemporal hollowing. Agenesis or hypogenesis of the corpus callosum may be seen, and small midline calcifications in the region of the septum pellucidum may be observed in patients with MDS (*140*). The cerebellum is notably normal in MDS (*146*).

115.3.2.1 Genetics and Biology. Identification of patients with MDS and monosomy 17p led to a suggestion that this locus may harbor the causative gene (*141*). This eventually led to the identification of *LIS1*, a gene that is deleted in MDS and deleted or mutated in ILS (*139*). Subsequent studies showed visible cytogenetic or submicroscopic deletions of 17p13.3 in more than 90% of MDS patients and in approximately 40% of patients with ILS (*140*). Point mutations as well as intragenic deletions and duplications of *LIS1* have also been identified in patients with ILS (*147–150*). What distinguishes the group of patients with *LIS1*-associated lissencephaly is a posterior predominance of the gyral abnormality, such that the posterior cortex is essentially agyric while there is typically a pachygyria pattern anteriorly. In ILS, the submicroscopic deletion is smaller than its counterpart in MDS (*151*,*152*), and so it has been suggested that MDS may represent a contiguous gene syndrome, with deletion of additional gene(s) being responsible for the dysmorphic features of MDS (*140*). There are eight genes that are consistently deleted in patients with MDS; deletion of the genes *CRK* and *YWHAE* appears to be associated with more severe lissencephaly (*153*). Animal studies have also shown that the 14-3-3 epsilon protein encoded by *YWHAE* is important for neuronal migration (*154*).

Virtually all known *LIS1* mutations are de novo; thus if a deletion or a mutation of the *LIS1* gene is identified in a patient, the recurrence risk is very low (*155*). There are rare cases in which one of the parents harbors a balanced translocation in the area involving the *LIS1* gene. In such cases, the risk is significantly higher, and up to 33% of the offspring having an abnormal genotype (i.e. deletion or duplication of 17p) and/or phenotype (*156*). Originally both Miller (*157*) and Dieker (*158*) reported familial cases of MDS, and later studies revealed translocations in both the families they described (*159*).

The normal cellular function of the LIS1 protein is thought to be related to regulation of microtubules. Microtubules, which are major components of the cytoskeleton, play a critical role in essential cellular processes, such as cell division and migration. LIS1 has been known to interact directly with microtubules and stabilize them. LIS1 also interacts with motor protein dynein (*160*) and regulates the microtubule-based molecular motor (*161–163*).

115.3.3 X-Linked Lissencephaly 1/ Subcortical Band Heterotopia

A familial, X-linked form of lissencephaly (LISX1; OMIM 300067) has also been identified and is associated with a higher recurrence risk than lissencephaly due to *LIS1* mutations. LISX1 manifests in affected hemizygous males as a disorder quite similar to MDS/ILS, with severe intellectual disability, intractable seizures, classical lissencephaly with pachygyria/agyria, agenesis of corpus callosum, and death during infancy (Figure 115-2) (*164*). This disorder manifests as a much milder phenotype in heterozygous females, who present with subcortical band heterotopia (SBH; also known as "double cortex" syndrome). SBH is characterized by symmetric stretches of gray matter found in the central white matter between the cortex and the ventricular surface, associated with intellectual disability and epilepsy. There is a wide range of phenotypic severity—both in terms of cognitive outcome and epilepsy—associated with SBH (*165*).

Although the MRI findings of the brain of LISX1 patients are generally quite similar to that of MDS/ILS, there is a notable difference in the pattern of malformation. The malformation is more severe posteriorly in patients with *LIS1* mutations and more severe anteriorly in patients with LISX1 (Figure 115-2) (*148*,*166*). In addition, a neuropathological study of two fetuses, one with a *LIS1* mutation and the other with a *DCX* mutation, showed different patterns of cortical lamination in these two conditions, suggesting possibly dissimilar pathogenetic mechanisms in MDS/ILS and LISX1 (*167*). Unlike MDS, there is no outward syndromic manifestation of LISX1 or SBH.

115.3.3.1 Genetics and Biology. Linkage analysis of pedigrees with LISX1/SBH localized the gene to Xq22 (*168*,*169*). The gene responsible for LISX1/SBH was identified and named *doublecortin* (*DCX*, OMIM 300121) (*170*,*171*). In one study, mutations of

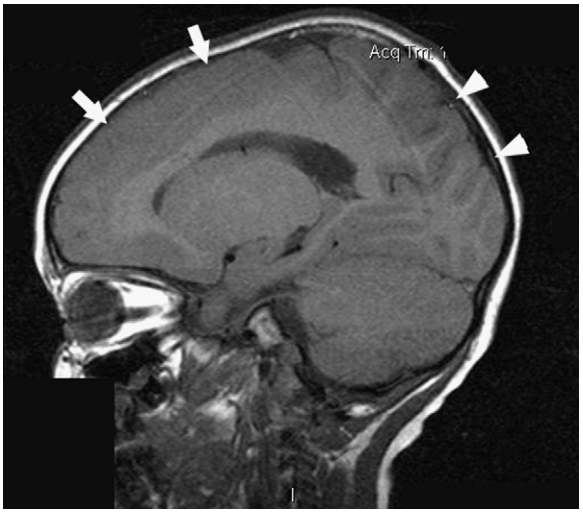

FIGURE 115-2 T1-weighted sagittal MRI image of a patient with X-linked lissencephaly 1 (LISX1) is shown. The anterior cortex almost completely lacks gyri (arrows), but the gyral pattern of the posterior cortex is relatively intact (arrowheads). This is typical of lissencephaly due to *DCX* mutations. In lissencephaly due to *LIS1* mutations, this anterior–posterior gradient is reversed (see text).

DCX were identified in all eight familial cases and in 18 of 47 (38%) sporadic cases of SBH (*172*). Another study found mutations of *DCX* in all 11 familial cases of SBH, and in 22 of 26 (85%) sporadic SBH cases (*173*). Although most of the reported *DCX* mutations are point mutations, intragenic deletions have been reported (*149*). Unlike *LIS1* mutations, in which the risk of a second affected child is low, recurrence of either LISX1 or SBH will be 50% if the mother is affected with SBH due to a *DCX* mutation. Therefore, in males with lissencephaly who do not show deletion or mutation of *LIS1*, mutation analysis of *DCX* should be considered. MRI examination of the mother may reveal SBH, particularly if the mother has epilepsy or cognitive difficulties. Maternal germline mosaic mutations in *DCX* have also been reported (*173*,*174*). Together, *LIS1* and *DCX* mutations have been estimated to cause the most cases (approximately 76%) of classical lissencephaly in the United States (*148*). There are likely to be other lissencephaly loci responsible in the rest of the patients. The presence of an autosomal recessive locus for lissencephaly has been suggested (i.e. Norman-Roberts syndrome; OMIM 257320) (*175*). It should also be noted that both male and female patients with SBH and somatic mosaic *DCX* mutations have been reported (*165*,*174*,*176*,*177*). Rare patients with mosaic mutations of *LIS1* presenting with SBH have also been reported (*178*). In more recent years, mutations in *DCX* have also been associated with a milder range of phenotypes, including nonsyndromic intellectual disability with normal MRI in females (*179*) and anterior-predominant pachygyria in males (*180*).

When compared to cases with *LIS1* mutations, cases with *DCX* mutations display variable neuropathological patterns, some with a six-layer cortex and others with an ill-defined four-layer cortex. In individuals with mutations in *LIS1*, linear disruptions of the gray–white matter junction have been observed; in contrast, individuals with mutations in *DCX* displayed more irregular disruptions of the gray matter–white matter junction as well as nodular heterotopias (*181*).

DCX is expressed in postmitotic neurons throughout the developing nervous system. The DCX protein has been shown to interact with and stabilize microtubules (*182–184*). Note that *LIS1* and *DCX*, two genes that lead to the phenotype of classical lissencephaly, are both involved in the regulation of microtubules. The structure of DCX includes two microtubule binding domains in the protein (*185*). Thus, regulation of microtubules appears to be essential for migration of cortical neurons.

115.3.4 Lissencephaly Associated with *TUBA1A* Mutations

Mutations in *TUBA1A*, which encodes the microtubule-related protein α-tubulin, have been associated with a wide range of cerebral malformations including lissencephaly (OMIM 611603) (*186*,*187*,*337*). The prototype of *TUBA1A*-associated lissencephaly includes additional abnormalities of the hippocampi, corpus callosum, brainstem, and cerebellum (*187*). Abnormalities in the basal ganglia have been seen as well in some cases (*188*). Histological findings in severe cases with mutations in *TUBA1A* include abnormal lamination of the cerebral cortex and hippocampi as well as heterotopic and misoriented neurons in the cortex (*188*). After several cases with varying degrees and patterns of lissencephaly were screened for mutations in *TUBA1A*, the spectrum of *TUBA1A*-associated lissencephaly has come to include a mild form with perisylvian pachygyria as well as a more severe form consisting of posteriorly predominant pachygyria (with a gradient similar to that seen in association with *LIS1* and *ARX*), microcephaly, cerebellar hypoplasia, and abnormalities of the anterior limb of the internal capsule (*186*,*189*). The associated phenotype is reported to include intellectual disability; the proportion of patients with mutations in *TUBA1A* with epilepsy is not yet reported but is expected to be very high.

While *TUBA1A* is relatively new to the lissencephaly genetic landscape, it is really not surprising, given the microtubule-associated roles of *LIS1* and *DCX*, that a gene encoding α-tubulin would be associated with a defect in migration resulting in lissencephaly. Interestingly, similar to what has been observed for *ARX*, there have been abnormalities in interneuron migration suggested by the observation of decreased numbers of interneurons in a fetus with a known mutation in *TUBA1A* (*188*).

115.3.5 X-Linked Lissencephaly 2 (X-Linked Lissencephaly with Abnormal Genitalia)

There is another form of X-linked lissencephaly (X-linked lissencephaly 2, also known as X-linked lissencephaly with abnormal genitalia; LISX2; OMIM 300215). In a typical patient with LISX2, lissencephaly is associated with agenesis of the corpus callosum and ambiguous or underdeveloped genitalia (*190–192*). The causative gene for this syndrome was identified as the Aristaless-related homeobox transcription factor gene, *ARX* (*193*). ARX has been shown to regulate tangential migration of interneurons (*193–196*). It is also implicated in regulation of neuronal proliferation (*193*,*195*). In addition to LISX2, mutations in the *ARX* gene can cause a wide variety of syndromes, ranging from severe brain malformations, such as hydranencephaly, to neurological disorders with apparently normal brain structure, such as West syndrome, nonsyndromic intellectual disability or autism (*197–199*). There seems to be some degree of genotype–phenotype correlation in that mutations that cause premature termination are more likely to be seen in patients with overt malformations and mutations that cause polyalanine expansion are commonly seen in patients without malformations (*197*).

While the pattern of lissencephaly associated with *ARX* mutations is a posterior-predominant agyria, with a gradient similar to what is seen in the setting of *LIS1* mutations, there are several features that may distinguish the two: (1) a cell-sparse layer is observed with LIS1, but brains from patients with mutations in *ARX* have only three cortical layers and lack a cell-sparse zone (*181*); (2) agenesis of corpus callosum is commonly seen with *ARX* mutations (*197*); and (3) the basal ganglia are noted to be small in patients with lissencephaly due to *ARX* mutations (*198*).

115.3.6 Lissencephaly with Cerebellar Hypoplasia

A variety of types of lissencephaly with cerebellar hypoplasia have been defined (*200*), and one of them, an autosomal recessive form of lissencephaly with severe hypoplasia of the cerebellum, has been characterized genetically (*201–203*). Since no postmortem studies on this condition have been published, it is unknown whether it resembles type I lissencephaly microscopically or whether it shows a unique histological pattern. Mutations in a gene called *reelin* (*RELN*) have been identified in two families with this condition (*204*). The *RELN* gene had previously been identified in mouse as causing the *reeler* mutation, which is characterized by disorganized cortical lamination and severe hypoplasia of the cerebellum (*205*). Therefore, it is likely that the histological pattern in humans reflect similar defects. Reelin is a protein secreted by Cajal-Retzius cells, which are the specialized neurons that reside in the uppermost layer of the cerebral cortex. Although there is evidence that Reelin acts as a "stop" signal for migrating neurons, the precise mechanism through which Reelin regulates neuronal migration is yet to be understood (*206*). Very-low-density lipoprotein receptor (VLDLR) and low-density lipoprotein receptor-related protein 8 (LRP8; also known as apolipoprotein E receptor -2) have been shown to act as receptors for Reelin (*207*), and mutations in the *VLDLR* gene have been associated with cerebellar hypoplasia similar to that seen with *RELN* mutations (*208*,*209*). Simplification of gyral pattern appears less severe in patients with *VLDLR* mutations.

115.3.7 Cobblestone Dysplasia

Cobblestone dysplasia is characterized by disorganized cortical layers, overmigration of neurons onto the outside of the brain through breaches in the pial surface, and gliovascular proliferation (*210*,*211*). The term "cobblestone" is applied because the ectopic neurons with gliovascular proliferation near the surface of the cortex give a bumpy cobblestone-like appearance. It has previously been called "type II lissencephaly" or "cobblestone lissencephaly." The gyral pattern seen on imaging studies varies widely, including polymicrogyria, pachygyria, and agyria, therefore, the term "cobblestone dysplasia" appears to be more appropriate.

Cobblestone dysplasia is the characteristic brain malformation observed in a group of disorders, sometimes referred to as "dystroglycanopathies," which includes three prototypic autosomal recessive disorders: Fukuyama congenital muscular dystrophy (FCMD), Walker-Warburg syndrome (WWS), and muscle-eye-brain disease (MEB). All three syndromes associated with cobblestone dysplasia affect the brain, muscle, and eye. As the genetic studies of these disorders progressed, it became clear that there was significant clinical and genetic overlap among these conditions. Since the fundamental biological defects in these disorders appear to be defects in glycosylation of α-dystroglycan, the term dystroglycanopathy has been coined.

FCMD is most prevalent in Japan, although rare cases have been reported from other countries (*212–214*). It presents with hypotonia during infancy, generalized weakness, intellectual disability, and occasionally seizures (*215*). WWS has been reported worldwide and has generally a much more severe phenotype. Patients with WWS often present with severe hypotonia and lethargy during the neonatal period. Median survival in one study was 9 months (*216*). Various forms of eye abnormalities are seen, including retinal nonattachment/detachment, retinal dysplasia, cataract, persistent hyperplastic primary vitreous, microphthalmia, and coloboma (*216–218*). MEB is prevalent in Finland, although it has been reported in many countries. Patients with MEB often present with neonatal hypotonia and weakness, which develops into spasticity and contractures (*219*). Severe intellectual disability is the

rule, and eye abnormalities include severe visual failure and myopia (*219*).

On imaging studies, regions of cobblestone dysplasia usually appear as agyric or pachygyric areas. In typical FCMD, the frontal lobes show polymicrogyria, and cobblestone dysplasia is limited to the temporo-occipital area (*220*,*221*). WWS presents more dramatically, with diffuse agyric or pachygyric areas (representing cobblestone dysplasia), enlarged ventricles, hypoplasia of the pons and cerebellar vermis, fusion of the superior and inferior colliculi, and a diffuse abnormality of the cerebral white matter (Figure 115-3) (*221*,*222*). Imaging findings of MEB are similar to that of WWS, but abnormalities are usually less extensive (*221–224*). Cerebellar polymicrogyria with or without small cysts can be seen in any of these disorders.

115.3.7.1 Genetics and Biology. Linkage mapping assigned the *FCMD* gene to 9q31 (*225*,*226*); subsequently the causative gene termed *FKTN* (*fukutin*) was cloned (*227*) and appears to encode a glycosyltransferase. Most (87%) FCMD-bearing chromosomes have been derived from a single mutation consisting of a retrotransposon insertion in the 3′ untranslated region, suggesting an ancestral founder mutation in the Japanese population (*227*). Patients who are compound heterozygotes, carrying this founder mutation and a point mutation, have been found to be more likely to have severe phenotypes, including a WWS-like phenotype (*228*). Patients who are homozygous for nonfounder mutation have been reported, and the phenotype resembles WWS (*229–231*). These data suggest that the Japanese founder mutation may represent a partial loss-of-function allele. Subsequently, mutations in a gene with sequence similarity to *FKTN*, *FKRP* (fukutin-related protein), have been identified in patients with WWS- and MEB-like phenotypes (*232*).

The first reported gene for the MEB phenotype was linked to 1p34-p32 (*233*). Subsequently, the responsible gene in this locus was identified as *POMGNT1* (protein O-mannose beta-1, 2-N-acetylglucosaminyltransferase) (*234*). The identification of an *MEB* gene as a glycosyltransferase made other glycosyltransferases potential candidate genes for this group of disorders. Indeed, another glycosyltransferase, *POMT1* (protein O-mannosyltransferases), was found to be mutated in some patients with WWS (*235*). However, *POMT1* mutations seem to account for only a minority of cases of WWS, possibly as low as 7% (*231*,*236*). Subsequently, mutations in several other genes have been associated with WWS and MEB-like phenotypes. These include *FKRP* (fukutin-related protein) (*232*,*237*), *POMT2* (*238–240*) and *LARGE* (*241–243*). In one series, nine of 27 European and American patients with WWS were accounted for by mutations in *POMT1*, *POMT2*, *FKTN* and *FKRP*, and five of those cases were due to *FKTN* mutations (*231*).

POMT1, POMT2 and POMGNT1 are glycosyltransferases, and although the biochemical functions of FKTN, FKRP and LARGE are not completely elucidated, they appear to play essential roles in α-dystroglycan glycosylation. Animal studies have suggested that functional disruption of dystroglycan may be central to the CNS pathogenesis of these disorders (*244*). Hypoglycosylation of α-dystroglycan has been shown in patients with FCMD and MEB, and this abolishes binding activity of dystroglycan for ligands such as laminin, neurexin, and agrin (*245*). Thus, it may be speculated that this defect in binding leads to loss of integrity of the pial surface and that subsequent overmigration of neurons through these breaches leads to the development of cobblestone dysplasia.

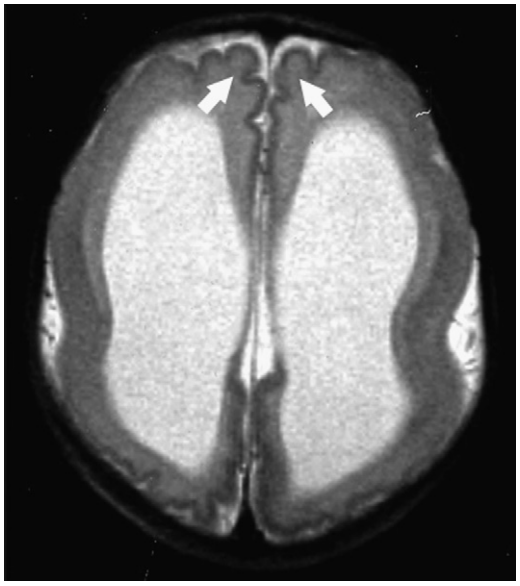

FIGURE 115-3 T2-weighted axial image of a patient with Walker-Warburg syndrome is shown. Enlarged lateral ventricles are evident. The gyral pattern seen here is mostly agyria (absence of gyri), but some areas show pachygyria (broadened gyri; arrows).

115.3.8 X-Linked Periventricular Heterotopia

Gray matter heterotopias are masses of well-differentiated neurons in abnormal locations, reflecting arrested radial neuronal migration. Periventricular heterotopia (PH) can be encountered as a sporadic condition, but there are several genetic syndromes in which heterotopias are a cardinal feature. One such syndrome is X-linked PH (OMIM 300049), for which many familial cases are known (*246–249*). In these pedigrees, typically only females were affected and there was a high rate of miscarriages among the affected females. These observations led to the suggestion that the condition was an X-linked disorder with prenatal lethality in males (*247*).

Females affected with X-linked PH typically present with epilepsy, commonly generalized tonic-clonic or complex partial seizures. Typical age of onset is before the mid-twenties, and the average age is around 15 years.

Intelligence is usually normal, although some patients have borderline intellectual disability, and dyslexia is remarkably common (*250*,*251*). An increased incidence of patent ductus arteriosus and stroke at young ages has been noted (*252*). Abnormalities in cardiac valve development have also been reported in some cases (*252*,*253*), and an increasing number of affected patients have vascular manifestations of Ehlers-Danlos syndrome (*254*).

Brain MRI of affected females typically shows bilateral PH nodules, which show the typical signal characteristics of normal gray matter. Pathologically, brains of females with X-linked PH show continuous bands or discontinuous nodules of gray matter along the periventricular region, consisting of well-differentiated cortical neurons (*255*). The heterotopic subependymal nodules of X-linked PH may initially be misdiagnosed as TSC nodules (*256*), but classical lesions of X-linked PH appear as roughly symmetric nodules as opposed to the less-confluent and not necessarily symmetric nodules of TSC.

115.3.8.1 Genetics and Biology. X-linked PH was mapped to distal Xq28 (*255*), and subsequently mutations in the *FLNA* (*filamin A*) gene were identified to be the cause (*252*). Mutations in *FLNA* have been identified in almost 100% of familial cases of X-linked PH (*257*,*258*) and 26% of sporadic patients with classical bilateral nodular PH (*257*). In rare instances, male patients with PH have *FLNA* mutations, but the majority of male patients are negative for *FLNA* mutations (*257*,*258*). *FLNA* mutations have also been identified in patients with PH and coexisting Ehlers-Danlos syndrome (OMIM300537) (*254*) and X-linked chronic idiopathic intestinal pseudo-obstruction with CNS involvement (OMIM300048) (*259*). In recent years, the clinical spectrum of *FLNA* mutations has expanded to include conditions in which non-CNS involvement predominates or in which no CNS involvement is noted. For example, *FLNA* mutations that preserve the reading frame have been shown to be associated with otopalatodigital syndrome types 1 (OMIM311300) (*260*) and 2 (OMIM304120) (*260*), frontometaphysial dysplasia (OMIM305620) (*260*), Melnick-Needles syndrome (OMIM309350) (*260*), FG syndrome-2 (OMIM300321) (*261*), terminal osseous dysplasia (OMIM300244) (*262*), and cardiac valvular dysplasia (OMIM314400) (*263*). This suggests that *FLNA* is involved in a broad range of organogenesis involving the nervous, skeletal, and cardiovascular systems. It has been speculated that the mutations associated with some of these syndrome may be gain-of-function mutations affecting specific protein interactions (*260*,*264*), unlike mutations associated with PH, which are probably loss-of-function mutations.

FLNA encodes a large cytoplasmic actin-binding protein that was originally identified in macrophages as a protein that precipitated actin (*265*). It had been shown to be essential for migration in non-neuronal cell types (*266*,*267*), but its role in neuronal migration had not been known prior to identification of mutation in patients with X-linked PH. *FLNA* is expressed by the cortical neurons during migration (*252*,*268*) and possibly regulates the actin cytoskeleton in response to the extracellular signals during neuronal migration (*269*).

115.3.9 Other Genetic Hetertotopia Syndromes

An autosomal recessive syndrome with heterotopia associated with microcephaly (OMIM 608097) was found to be caused by mutation in the ADP-ribosylation factor guanine nucleotide-exchange factor-2 gene (*ARFGEF2*) (*270*). This gene functions in vesicle and membrane trafficking from the trans-Golgi network (TGN) and appears to be essential for proliferation of neuroblasts and migration of postmitotic neurons (*270*). PHs have been seen in association with various chromosomal anomalies. These include chromosome 5p anomalies (*271*), 5q deletion (*272*), 7q11.23 deletion (*273*), and 1p36 deletion (*273*,*274*).

115.4 MALFORMATIONS DUE TO ABNORMAL CORTICAL ORGANIZATION

115.4.1 Polymicrogyria

Polymicrogyria refers to a cortical malformation characterized by numerous small gyri. Clinical presentations of polymicrogyria depend on the extent and location of the abnormal cortex. When the abnormality is diffuse, severe developmental delay is the rule, but when it is focal, developmental delay is less severe (*104*). Some individuals with small regions of focal polymicrogyria have normal intelligence. Seizures are common in both groups. On MRI, small meandering gyri of polymicrogyric cortex may appear as thickened cortex, and it may be difficult to distinguish from "pachygyria" (thickened cortex). Irregularity of the junction between the cortex and white matter is usually evident with high-resolution imaging (*275*,*276*).

In recent years, several distinctive syndromes of polymicrogyria have emerged (*277*). These syndromes, which are mainly distinguished by characteristic distributions of polymicrogyric cortex, include bilateral frontoparietal polymicrogyria (BFPP; OMIM 606854) (*278*), congenital bilateral perisylvian syndrome (CBPS; OMIM 300388; also known as bilateral perisylvian polymicrogyria (BPP)) (*279*), bilateral generalized polymicrogyria (BGP) (*280*), and bilateral occipital polymicrogyria (OMIM 612691) (*281*).

BFPP is associated with symmetrical distribution of polymicrogyria in the frontal and parietal cortex (Figure 115-4). The clinical presentation includes moderate to severe developmental delay, seizures (usual onset after 4–5 years), bilateral pyramidal and cerebellar signs, and dysconjugate gaze (*278*). CBPS is characterized by

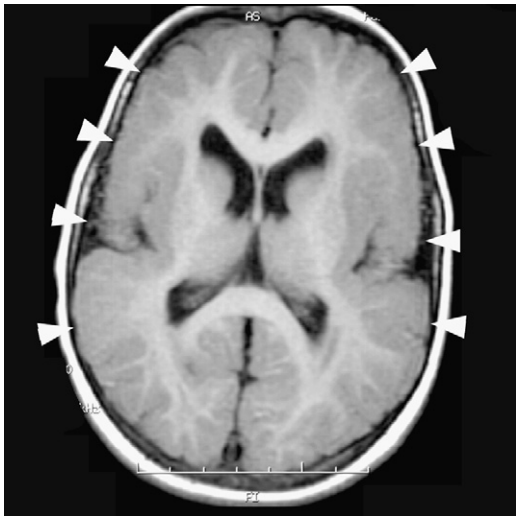

FIGURE 115-4 T1-weighted axial MRI image of a patient with bilateral frontoparietal polymicrogyria is shown. The frontoparietal cortex shows an abnormal gyral pattern (arrowheads), which represents clusters of abnormal small gyri. The occipital cortex appears typically spared in this condition, and appears relatively normal in this image. Mutations in *GPR56* are responsible for the condition.

diplegia of the facial, pharyngeal, and masticatory muscles, which can be explained by the location of abnormal cortex (*282*). Intellectual disability is common, but the severity ranges from mild to severe. Epilepsy is also common, and typically has its onset between 4 and 12 years of age (*283*). BGP is characterized by motor and cognitive delay, and seizures are frequent. Dysconjugate gaze, which is commonly seen in BFPP, or pseudobulbar palsy, which is a hallmark of CBPS, is not typically seen in BGP (*280*). A comprehensive review of the clinical features of 328 cases of polymicrogyria revealed that seizures occurred in 78%, global developmental delay in 70% and microcephaly in 50%; generally, the more severely affected children had more widespread polymicrogyria and earlier age at presentation with epilepsy or other neurological symptoms (*277*).

115.4.1.1 Genetics and Biology. Polymicrogyria is usually encountered as a sporadic condition; however, it has become evident that there are distinct genetic syndromes with polymicrogyria. Polymicrogyria in association with chromosome 22q11 deletions have been well documented (*284*,*285*,*338*), although only a minority of the patients with 22q11 deletion have polymicrogyria. Furthermore, recurrent copy number variations at 1p36.3, 2p16.1-p23.1, 4q21.21-q22.1, 6q26-q27, and 21q2 have been reported in patients with polymicrogyria (*286*), suggesting that genes in these regions may be involved in brain development, particularly proper cortical organization. It is important to note that the majority of individuals with polymicrogyria associated with these copy number variants displayed dysmorphic features that today would prompt evaluation with a chromosomal microarray to assess for deletions or duplications.

BFPP, originally described under several different monikers, is often seen in consanguineous pedigrees, suggesting autosomal recessive inheritance (*202*,*287–291*). BFPP was mapped to 16q12.2-21 (*292*), and subsequently the causative gene was identified (*293*). The gene mutated in BFPP, *GPR56*, encodes a G-protein coupled receptor, whose ligand is not identified yet. GPR56 appears to be essential for maintaining the integrity of pial basement membrane (*294*), and therefore the pathogenesis of BFPP appears to overlap with that of cobblestone dysplasia (see Section 115.3.7). BFPP is increasingly recognized as sharing radiographic and pathologic features with cobblestone dysplasia (*295*).

Recently, mutations in *LAMC3*, encoding a laminin protein that is characteristic of the pial basement membrane, has also been discovered in association with polymicrogyria in the occipital region (*296*). This adds to the evidence suggesting that disruption of the pial basement membrane is a common cause of polymicrogyria.

There have been many reports of familial cases of CBPS (*279*). Many pedigrees were found to be consistent with an X-linked mode of inheritance or autosomal dominant inheritance with incomplete penetrance, and genetic loci for CBPS have been identified at Xq28 (*297*) and Xq27 (*298*); however, other genetic loci may exist for this syndrome. Some patients with BGP are siblings and/or born to consanguineous parents, suggestive of autosomal recessive inheritance (*280*). In familial BGP cases, linkage to the BFPP locus on 16q has been ruled out, but the locus for BGP has not been identified (*280*).

There is also evidence that prenatal insults, such as hypoxic-ischemic injury, can lead to polymicrogyria. Polymicrogyria in some of these cases has been suggested to result from postmitotic encephaloclastic lesion (*299*,*300*), but animal studies have indicated that cortical injuries resulted in polymicrogyria only when they occurred during the course of migration (*301–303*). Other types of intrauterine insults (e.g. cytomegalovirus infection) and metabolic disorders (see below) have been associated with polymicrogyria as well, but genetic forms of polymicrogyria always need to be considered. For example, bandlike calcification of the brain with simplified gyral pattern and polymicrogyria (OMIM 251290), which resembles TORCH (Toxoplasmosis, Other, Rubella, Cytomegalovirus, Herpes simplex virus) infection and sometimes referred to as pseudo-TORCH syndrome, is associated with mutations in a tight-junction protein gene, *OCLN* (*304*). Interestingly, a mutation in another tight-junction protein gene *JAM3* has been reported to cause calcification of the brain (OMIM 613730) (*305*). Patients with a mutation in *JAM3* often had severe perinatal intracranial hemorrhage, but no obvious polymicrogyria was noted.

Two families have been reported with perisylvian polymicrogyria and mutations in the sushi-repeat-containing gene *SRPX2*, located at Xq22; one mutation (N327S) was found in a French family presenting with rolandic seizures, oral and speech dyspraxia, and variable degrees of intellectual disability, and a second mutation (Y72S)

was reported in a male patient with seizures of the rolandic area and BPP whose female relatives with the same mutation had only mild intellectual disability without polymicrogyria (306).

115.4.2 "Tubulinopathies" and Polymicrogyria

As mentioned above, *TUBA1A* is a gene encoding a microtubule-related protein that is associated with brain malformations, typically lissencephaly with other features. Recent work suggests that mutations in *TUBA1A* are also responsible for some cases of BPP (187,189). Although it is not a common cause of BPP, the association between this gene—known to be involved in cortical migration—and a defect such as polymicrogyria that is thought to reflect a disorder of later cortical organization speaks to the idea that many of the genes in brain development are important through multiple stages of brain development. Along the same lines, mutations in the gene encoding β-tubulin, *TUBB2B*, have been reported in five cases of asymmetrical polymicrogyria (OMIM 610031) (307). Mutations in *TUBA8* have been implicated in a form of polymicrogyria associated with optic nerve hypoplasia (OMIM 613180) (308). Additionally, mutations in the gene *TUBB3* have been seen in cases of frontally predominant polymicrogyria associated with basal ganglia dysmorphism, corpus callosum abnormalities, and mild brainstem hypoplasia (309) without the feature of congenital fibrosis of the extraocular muscles reported in the original description of *TUBB3* mutations (310).

115.4.3 Schizencephaly

The term "schizencephaly" (OMIM 269160) was coined by Yakovlev and Wadsworth in 1946 and refers to a brain malformation characterized by full-thickness cleft of the cerebral mantle (311,312). The walls of the clefts are usually lined by polymicrogyric cortex. As Yakovlev and Wadsworth proposed, schizencephaly can be divided into two subtypes, namely closed-lip schizencephaly and open-lip schizencephaly. In closed-lip schizencephaly, two walls are in apposition and form a so-called "pial-ependymal seam." On the other hand, in open-lip schizencephaly the two walls are apart and the space between the two walls is filled with cerebrospinal fluid (CSF) (Figure 115-5). The clinical presentation varies depending on the extent and location of anatomical abnormalities. Closed-lip schizencephaly often presents with hemiparesis or motor delay, and open-lip schizencephaly may present with the same features as well as seizures (313). Generally, the severity of motor and/or cognitive impairment is related to the extent of anatomic malformation; however, the presence or severity of epilepsy may not be predicted from the extent of the anatomical abnormality. Although schizencephaly is usually seen as sporadic cases, rare familial cases have been reported (314–318).

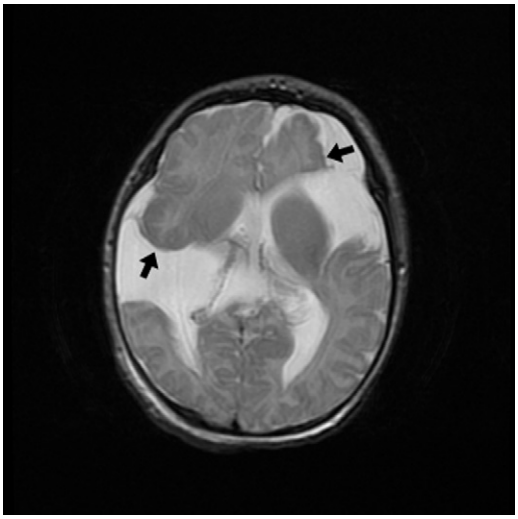

FIGURE 115-5 T2-weighted axial MRI image of a patient with bilateral open-lip schizencephaly is shown. The walls of the full-thickness clefts are lined by abnormal cortices (arrows), which often prove to be polymicrogyria histologically.

The presence of *de novo* heterozygous mutations in the *EMX2* gene has been reported in sporadic and familial cases of schizencephaly (319–321); however, subsequent sequencing effort failed to identify any pathogenic *EMX2* mutation in a total of more than 100 patients with schizencephaly (322,323). Thus the role that *EMX2* plays in pathogenesis of schizencephaly is not entirely clear. Recently, a few patients with *WDR62* mutations were found to have schizencephaly as well as microcephaly (32,34), but the proportion of cases of schizencephaly caused by *WDR62* mutation is not known. Schizencephaly can also definitely be caused by nongenetic etiology, such as the death of monozygotic cotwin (324), and is associated with environmental risk factors, such as in utero exposure to warfarin, alcohol and cocaine and young maternal age (324), to a much greater extent than any other cortical malformation, suggesting a substantial role for nongenetic factors as well.

115.5 MALFORMATIONS OF CORTICAL DEVELOPMENT, NOT OTHERWISE CLASSIFIED

115.5.1 Malformations Secondary to Inborn Errors of Metabolism

Typically, inborn errors of metabolism cause degenerative cerebral lesions; however, several metabolic disorders are associated with developmental malformations of the cerebral cortex. For example, neuronal migration abnormalities, particularly perisylvian pachygyria-polymicrogyria, are a prominent feature of Zellweger syndrome (325–328). Pathological studies have shown abnormal pleomorphic cytosomes, presumably the results of excessive very-long-chain fatty acids, in astrocytes, neuroblasts, immature neurons and radial glia,

suggesting linkage between the underlying biochemical abnormality and migrational disturbances (*326*). Studies of an animal model of Zellweger syndrome have suggested that peroxisomal function in both brain and extraneuronal tissues is important to the normal neuronal migration (*329*).

Other inborn errors of metabolism associated with developmental disorders of the cerebral cortex include multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type II; OMIM 231680) (*330*) as well as mitochondrial disorders and disorders of pyruvate metabolism (*331–334*). The pathogenesis of cortical dysgenesis in these disorders is not well understood. Amish lethal microcephaly (OMIM 607196) is a metabolic disorder reported among the Old Order Amish of Lancaster County, Pennsylvania. The patients have severe congenital microcephaly and 2-ketoglutaric aciduria; they typically die within the first year of life. This is one of the few known metabolic disorders that are associated with congenital, rather than postnatal, microcephaly. The causative gene is *SLC25A19* (*335*), which may be involved in mitochondrial thiamine pyrophosphate transport and affects the function of the α-ketoglutarate complex (*336*). Other metabolic causes of congenital microcephaly include maternal phenylketonuria and phosphoglycerate dehydrogenase deficiency (*24*).

115.6 CONCLUSIONS

Recent years have seen dramatic progress in the area of genetic malformations of the cerebral cortex. As more and more genes for brain malformations are identified, clinical syndromes are being redefined based on their underlying genetic basis. Although some of the disorders presented here are rare, they collectively account for a large number of patients with neurological disabilities. Identification of the causative genes has already led us toward the development of genetic testing and better genetic counseling for the patients and their families. In addition, studying the functions of these genes continues to lead to a better understanding of biological mechanisms of the human brain development. There still remains a stunning diversity of genetic disorders of cortical development that are yet to be characterized and studied, and each year brings further progress in understanding the genetic basis of many of those disorders. With the advent of next-generation sequencing, we expect to see an ever-increasing number of genes involved in brain development identified and characterized through the study of human cerebral malformation syndromes.

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Online Mendelian Inheritance in Man, http://www.ncbi.nlm.nih.gov/omim.
GeneTests, http://www.ncbi.nlm.nih.gov/sites/GeneTests/.
Christopher, A. Walsh Laboratory, http://www.walshlab.org/.

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Dr Christopher A Walsh, MD, PhD is Bullard Professor of Pediatrics and Neurology at Harvard Medical School, Chief of the Division of Genetics at Boston Children's Hospital, and an Investigator of the Howard Hughes Medical Institute. He completed his MD and PhD degrees at the University of Chicago. After a neurology residency and chief residency at Massachusetts General Hospital, he completed a fellowship in genetics at Harvard Medical School. He joined the faculty at Harvard Medical School in 1993 and has held the Bullard Professorship since 1999. Dr Walsh's research has focused on the development, evolution, and function of the cerebral cortex. He has pioneered the analysis of human genetic diseases that disrupt the cerebral cortex, including autism, intellectual disability, seizures, and cerebral palsy, identifying genetic causes for more than a dozen brain diseases of children. Among his awards are a Jacob Javits Neuroscience Investigator Award (National Institute of Neurological Disorders and Stroke), the Dreifuss-Penry Award Epilepsy Research Award (American Academy of Neurology), the Derek Denny-Brown Award and the Jacoby Award (American Neurological Association), the Research Award (American Epilepsy Society), and the Wilder Penfield Award (Middle Eastern Medical Assembly). He is an elected member of the American Neurological Association, the American Association of Physicians, and an elected fellow of the American Association for the Advancement of Sciences.