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Malformations of cortical development: clinical features and genetic causes

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Abstract

Malformations of cortical development are common causes of developmental delay and epilepsy. Some patients have early, severe neurological impairment, but others have epilepsy or unexpected deficits that are detectable only by screening. The rapid evolution of molecular biology, genetics, and imaging has resulted in a substantial increase in knowledge about the development of the cerebral cortex and the number and types of malformations reported. Genetic studies have identified several genes that might disrupt each of the main stages of cell proliferation and specification, neuronal migration, and late cortical organisation. Many of these malformations are caused by de-novo dominant or X-linked mutations occurring in sporadic cases. Genetic testing needs accurate assessment of imaging features, and familial distribution, if any, and can be straightforward in some disorders but requires a complex diagnostic algorithm in others. Because of substantial genotypic and phenotypic heterogeneity for most of these genes, a comprehensive analysis of clinical, imaging, and genetic data is needed to properly define these disorders. Exome sequencing and high-field MRI are rapidly modifying the classification of these disorders.

Introduction

The development of the human cerebral cortex is a complex and tightly organised process. Disruption of any of the overlapping steps that contribute to this process can result in a wide range of developmental disorders. Many of these disorders are recognised as malformations in studies of brain imaging and collectively comprise a class of disorders that we designated as malformations of cortical development (MCD). This term was introduced to include disorders with defective cortical development in which the cortical ribbon itself appears normal (specifically some types of microcephaly, megalencephaly, and heterotopia).[1]

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Declaration of interests

We declare no competing interests.

The classification scheme for MCD is based on the developmental steps at which the process is first disturbed, the underlying genes and biological pathways disrupted, and – when more objective data are not available – imaging features.[1–4] This system classifies MCD into three major groups that recapitulate the main developmental steps as malformations of cell proliferation, neuronal migration, or postmigrational cortical organisation and connectivity. The ideal classification should (and eventually will) rely on knowledge of biological pathways, which is not available at present. Indeed, recent advances suggest that boundaries between disorders of neuronal proliferation, migration, or subsequent cortical organisation are fading, as emphasised by the recent identification of a broad range of malformations with mutations in *WDR62*, *DYNC1H1*, and *TUBG1*.[5–8] These findings support the notion that MCD-related genes are implicated in many developmental stages that are genetically and functionally interdependent.

In this Review, we address the most difficult issues with classification, review the most common clinical presentations across MCD, provide detailed descriptions of the most common and conceptually important MCD, and discuss the genes associated with these malformations. We address these points from both a general perspective and a more specific phenotype-based approach for the most common of these disorders.

Limits in classification of MCD

Although the classification of MCD has advanced substantially during the past decade, in practice only a few categories are used, including lissencephaly, polymicrogyria, schizencephaly, focal cortical dysplasia (FCD), and periventricular nodular heterotopia. However, emerging evidence suggests that MCD are far more heterogeneous than this classification suggests, especially cases of irregular or pebbled cortical surfaces that are usually classified as polymicrogyria, even when the typical curvilinear microsulci are not seen. One example is so-called bilateral frontoparietal polymicrogyria. Reports both before and after identification of *GPR56* as the causal gene of this MCD showed a cobblestone-type cortical malformation associated with defects in the pial basement membrane.[9,10] This disorder is now referred to as bilateral frontoparietal cobblestone malformation, but use of the term polymicrogyria persists.

Individuals classified as having polymicrogyria have such diverse clinical courses and outcomes, causes and recurrence risks, associated malformations and syndromes, and imaging and neuropathological abnormalities as to render the term no more specific than that of intellectual disability. Further, the borders between MCD now classified as separate malformations have become blurred, because the new tubulinopathies can present as either lissencephaly-like or a polymicrogyria-like MCD (appendix). Enough data have accumulated to allow reclassification of some polymicrogyria-like CD as malformations due to generalised abnormal transmantle migration, similar to classic lissencephaly.[4]

MCD would ideally be classified with use of a comprehensive approach that includes data from several different disciplines. However, this system is difficult because specialties such as molecular genetics generate large amounts of new data, whereas other specialties such as neuropathology and developmental neurobiology lag behind, unless surgical removal of affected human tissues is possible or animal models are available.[11–14]

Brain imaging

Most MCD can be differentiated by moderate-to-high quality MRI scans (figure 1). The key features to look for include distribution and severity of the MCD, the cortical surface and border between white and grey matter (smooth or irregular), cortical thickness, and associated brain malformations. We summarise the key differences in imaging of different MCD in the appendix. Our preliminary experience suggests that ultra-high field 7 Tesla imaging will improve characterisation of localised forms of polymicrogyria and FCD (figure 2), although its usefulness to detect regions of abnormal cortical development after negative standard 3T MRI has not been systematically assessed yet.

Knowledge of the main morphological features of the normal pattern of cortical development has helped the prenatal diagnosis of some MCD, including regional polymicrogyria at an early sulcation stage with use of either neurosonography[15] or fetal MRI.[16] Diagnoses can sometimes be made before 24 weeks of gestation, and can help to select the most appropriate genetic testing and counseling. For these reasons, detailed neurosonographic examination or fetal brain MRI is recommended even when minor CNS anomalies, or even non-CNS anomalies, are detected by previous ultrasound.[15] However, these imaging techniques also have serious limitations, because of the risk of detection of non-pathological variants, very little association with neuropathological findings, and complexities in provision of appropriate counseling.

Clinical presentation, course, and outcome MCD as a group have highly variable clinical presentations and burden of disability, and can be loosely separated into two large, although overlapping, groups: early diffuse MCD with poor developmental and neurological outcomes, and later-onset MCD with variable outcomes due to patchy brain involvement.

Severe disabilities

Most children with diffuse MCD first come to medical attention because of early feeding problems, seizures, or global developmental delay. Others might be recognised because of abnormally small or large head size, hydrocephalus, or other congenital anomalies. Children with these clinical presentations have severe congenital microcephaly, dysplastic megalencephaly (including hemimegalencephaly), lissencephaly, cobblestone malformation, polymicrogyria-like malformations, or classic polymicrogyria. The most severely disabled children can have severe deficits in language development and social interactions, stereotyped or other involuntary movements, autonomic (especially gastrointestinal) dysregulation, abnormalities in mood, sleep, and attention, and visual and hearing loss. Most have severe neurological disabilities and high risk for a reduced life span.

Less severe disabilities

By contrast, children or adolescents with FCD often have normal neurological skills and are brought to medical attention after the onset of focal epilepsy, which will often be their only problem and the only determinant of their long-term prognosis. Other less severely affected individuals are likely to have mild-to-moderate learning disability, epilepsy of variable severity, and attention deficit. The less severe disabilities are a result of bilateral but patchy malformations such as periventricular nodular or subcortical heterotopia, mild forms of

subcortical band heterotopia, or polymicrogyria. The overall burden of neurological disability will depend on these clinical features, which can be combined with any degree of severity. Although few detailed studies comparing the type and distribution of MCD with the outcome have been done,[17–25] based on our personal experience of assessing hundreds of children with MCD we have developed general guidelines useful for prediction of the outcomes in children with MCD (table 1).

Genes, biological pathways, and mosaicism

So far, more than 100 genes are reported to be associated with one or more types of MCD. The biological pathways include cell-cycle regulation at many steps (especially mitosis and cell division), apoptosis, cell-fate specification, cytoskeletal structure and function, neuronal migration and basement-membrane function (figures 3, 4), and many inborn errors of metabolism. Metabolic errors include some disorders of mitochondrial and pyruvate metabolism, non-ketotic hyperglycaemia, and protein glycosylation, in addition to many different defects of peroxisomal biogenesis.[4]

Importantly, a subset of MCD genes – especially those associated with megalencephaly – are associated with postzygotic (ie, mosaic) mutations.[12,13,26] Several patients with mosaic mutations of FLNA, LIS1 (also known as PAFAH1B1), or DCX have fairly mild phenotypes.[27–31] Also, subcortical nodular heterotopia is frequently unilateral or asymmetrical. We hypothesise that many additional types of megalencephaly, dysplastic megalencephaly (including classic hemimegalencephaly), FCD, lissencephaly, polymicrogyria, and heterotopia will prove to be caused by mosaic mutations.

Megalencephaly, dysplastic megalencephaly, and FCD type 2

Overview

The term megalencephaly refers to an abnormally large brain that exceeds the mean for age and gender by 2 SD (table 2).[39] In practice, it is a useful term for syndrome diagnosis for brain sizes more than 3 SD above the mean, because many individuals with so-called benign familial (anatomical) megalencephaly fall just below this range of +3 SD. In this Review, we use megalencephaly to refer to brains that are +3 SD or larger. Megalencephaly has most often been classified simply as a disorder of brain size, but recent studies have shown that megalencephaly with normal cortex by imaging, megalencephaly with polymicrogyria, and dysplastic megalencephaly (including classic hemimegalencephaly) can all result from mutations of the same genes in the PI3K-AKT pathway.[12,13,26] Thus, separation of megalencephaly syndromes on the basis of appearance of the cerebral cortex might not represent the underlying biology.

Pathological changes

Among patients with anatomical megalencephaly – a term that excludes metabolic forms – substantial clinical heterogeneity and several different pathological types have been described. Many anatomically large brains have a normal appearance other than increased thickness of brain structures, although few recent studies have been reported.[40,41]

Brain imaging in other individuals with megalencephaly shows diffuse or perisylvian polymicrogyria (figure 1C), although few pathological data are available except for thanatophoric dysplasia. In this disorder, the cortical malformation consists of broad gyri and deep sulci with an atypical polymicrogyria-like cortical malformation at the depth of sulci.[35,36] Heterotopic nests of neuroblasts immunoreactive for nestin and Ki-67 (also known as MKI67) occur in the intermediate and marginal zones, resembling the overproduction of intermediate progenitor cells in mice.[36,42]

The most severe cortical dysplasias associated with megalencephaly have been described in hemimegalencephaly. However, our experience suggests that the term hemimegalencephaly is a misnomer. In many affected individuals less than one whole hemisphere is affected (so-called hemi-hemimegalencephaly), but in others the abnormality involves more than one entire hemisphere.[43] We therefore prefer the term dysplastic megalencephaly to include all forms of segmental brain overgrowth with cortical dysplasia. The pathological changes reported in dysplastic megalencephaly include atypical pachygyria that can affect one or several lobes of the brain, most of one hemisphere, and sometimes one hemisphere and part of the other. The histological changes are similar if not identical to those in FCD type 2, which is characterized by cortical dyslamination and dysmorphic neurons without (type 2a) or with (type 2b) balloon cells, blurred junctions between grey and white matter, and increased heterotopic neurons in white matter.[14,44,45] In both FCD types 2a and 2b, dysmorphic neurons have enlarged cell and nucleus diameters, abnormally aggregated and peripherally displaced Nissl substance, and phosphorylated and non-phosphorylated neurofilament accumulation in the cytoplasm.[14] Balloon cells present with a large cell body, glassy eosinophilic cytoplasm that lacks Nissl substance, often several nuclei, and usually no cell lineage determination into glial or neuronal cells. FCD type 2 also features substantial blurring of the junctions between grey and white matter, and reduced myelination. A recent classification consensus also identified FCD type 1, which refers to isolated lesions presenting either as radial (FCD type 1a) or tangential (FCD type 1b) dyslamination of the neocortex, microscopically identified in one or multiple lobes; FCD type 3, which occurs in combination with hippocampal sclerosis (FCD type 3a), with epilepsy associated tumours (FCD type 3b), adjacent to vascular malformations (FCD type 3c), or in association with epileptogenic lesions acquired in early life (FCD type 3d).[14]

The histological changes in dysplastic megalencephaly seem to be split evenly between types 2a and 2b, and also include areas of polymicrogyria.[28]

The highly focal and variable nature of FCD type 2b, and the pathological resemblance to tubers in tuberous sclerosis, led to the hypothesis that somatic mosaic mutations of genes that encode proteins in the mTOR pathway, which includes *TSC1* and *TSC2* that cause tuberous sclerosis, were implicated in FCD.[46] In support of this hypothesis, several sequence variants in *TSC1* were noted more often in FCD type 2b than in control brains, and loss of heterozygosity of *TSC1* was reported in the brains of 11 of 24 patients with FCD type 2b.[47] Furthermore, one patient with FCD type 2b had a mosaic mutation in *PTEN*.[38]

Findings from a 2012 study[48] suggested that FCD type 2b but not FCD type 2a or cortical tubers in patients with tuberous sclerosis was associated with expression of human-

papillomavirus 16 E6 oncoprotein in large balloon cells, but not in other dysplastic cells. However, this finding needs confirmation from other groups, because it suggests embryonic infection in the first trimester of a small number of neural progenitors, which would be a new mechanism without any experimental support. Further, the investigators reported evidence of human papillomavirus in all patients studied, which would make infection the only cause of FCD type 2b in that series. This hypothesis seems unlikely in view of emerging data about genes in the mTOR pathway.

Brain imaging

The most common cortical malformation in megalencephaly is perisylvian polymicrogyria that looks very similar to perisylvian polymicrogyria in patients with normal or small head size (figure 1C). The cortical changes in dysplastic megalencephaly are severe and consist of enlargement of part or all of one hemisphere (or less often bilateral asymmetrical involvement) with no consistent preference for which lobes of the brain are enlarged (figure 1B). Other key changes include poor differentiation between grey and white matter, enlargement of deep structures in grey matter that displace the surrounding white matter and ventricles, variable hypointense and hyperintense T2-weighted abnormalities in white matter in the central and subcortical regions, and asymmetrical enlargement of the lateral ventricle with the larger ventricle usually on the more dysplastic side.[49]

Patients with FCD usually have enlarged gyri with either smooth or irregular cortical surface and increased subcortical signal intensity. Some individuals with FCD type 2b have migration tracts underlined by hyperintense radially oriented white-matter bands that extend from the dysplastic cortex to the periventricular region, which has been termed transmantle dysplasia (figure 1D).[50]

Clinical features

The developmental and health complications of megalencephaly differ widely. The most common problems include developmental delay, intellectual disability, and seizures that can start early in life and become intractable.

Children with diffuse symmetrical or mildly asymmetrical megalencephaly, with or without associated polymicrogyria, have large head size at birth that soon exceeds +3 SD.[51] Their early development is delayed, and later cognitive development varies from normal to severe intellectual disability. However, most individuals function in the upper half of this wide range, and we have met gainfully employed adults with even severe megalencephaly. Most patients with megalencephaly have mild-to-moderate hypotonia in infancy that slowly improves, especially in individuals with mild dysplasia of connective tissue. Seizures can begin at any time in childhood, but about 40% of children in our initial series had seizures with onset from the first days of life to 4 years.[51] We expect the incidence to rise as our cohort ages. Only 3 of 42 children had infantile spasms and 3 others had intractable seizures, making intractable epilepsy much less frequent than in the dysplastic megalencephaly group. Some of these children also had hydrocephalus, and cerebellar tonsillar ectopia with or without Chiari malformation.

Individuals with dysplastic megalencephaly (a group that includes hemimegalencephaly) typically have early developmental delay and more severe intellectual disability than do those with diffuse symmetrical or mildly asymmetrical megalencephaly. Epilepsy usually begins in the first weeks or months of life and can include infantile spasms and other epileptic encephalopathies. Intractable epilepsy is associated with a worse developmental outcome than is controllable epilepsy.

In almost all patients with FCD type 2, the lesion is detected after onset of focal epilepsy. Early seizure onset has been associated with infantile spasms with asymmetrical or focal features.[52] FCD type 2 is a frequent cause of focal status epilepticus and, together with FCD type I, is the most common pathological substrate in surgical series of epilepsy.[11] Developmental delay, cognitive disability, and focal neurological deficits are only reported with extensive areas of FCD.

Syndromes and genetics

A growing number of syndromes and genes have been associated with megalencephaly, especially with more severe phenotypes. Megalencephaly without cortical malformations occurs in benign autosomal dominant macrocephaly, a poorly defined disorder. The well-established syndromes with megalencephaly include neurofibromatosis type 1 due to *NF1* microdeletions that also involve the *RNF135* gene and Sotos syndrome (with *NSD1* mutations), Weaver syndrome (with *EZH2* mutations), in addition to Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome, and severe megalencephaly with autism (all three with *PTEN* mutations). Several other rare disorders are associated with megalencephaly, including deletion 10q22q23 or duplication 1q21.1 or 2p24.3.

Megalencephaly with polymicrogyria occurs in megalencephaly-capillary malformation syndrome (with mutations of *PIK3CA*) and megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome (with mutations of *PIK3R2* or *AKT3*),[51] and may be seen in patients with Weaver syndrome as well.[32] Dysplastic megalencephaly most often occurs without syndromic features, and has recently been associated with mosaic mutations of *PIK3CA*, *AKT3*, and *MTOR*.[12] Dysplastic megalencephaly has also been associated with the linear nevus sebaceous syndrome (also known as Schimmelpenning syndrome), and also rarely with CLOVES syndrome (congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies), tuberous sclerosis, hemi hypertrophy, and hypomelanosis of Ito.[43,54]

The causes of FCD types 2a and 2b are not known and remain controversial. However, these disorders are included in this Review because the pathological changes are the same as are those reported in dysplastic megalencephaly and tuberous sclerosis.

Tubulinopathies and related disorders

Classic lissencephaly and polymicrogyria have long been thought of as distinct disorders, but in recent reports lissencephaly and polymicrogyria-like cortical malformations have been associated with mutations of the same genes (tubulin or tubulin-related genes) that function during the early stages of neuronal proliferation, migration, differentiation, and axonal

guidance (ie, much earlier than the genes usually associated with polymicrogyria and schizencephaly).[8,55,56–58] The full range of these malformations is not yet understood, but they vary from severe lissencephaly with cerebellar hypoplasia to much less severe malformations (tables 3, 4; appendix). In view of the common pathophysiological mechanisms characterising tubulinopathies, we limit this discussion to tubulinopathies and consider classic lissencephaly, subcortical band heterotopia, and polymicrogyria in separate sections.

Pathological changes

Available pathological studies are limited to fetal brains, with findings showing severe defects in neuronal migration resulting in absent cortical lamination, radial columnar heterotopia, ectopic neurons in white matter and the leptomeningeal spaces because of overmigration through gaps in the pial basement membrane, and defects in axonal transport.[56,57] Some features, especially radial columnar heterotopia and neuronal overmigration, are not typical of classic lissencephaly or classic polymicrogyria. Findings from studies[58] of homozygous mouse mutants showed thinning of the cortical epithelium, which is substantially more severe in the caudolateral portion of the telencephalon, because of a major increase in apoptosis.

Brain imaging

The malformation varies from extreme lissencephaly with completely absent gyri, total agenesis of the corpus callosum, and severe cerebellar hypoplasia (figure 1E), to less severe lissencephaly with moderate-to-severe cerebellar hypoplasia (not shown), to classic lissencephaly (figure 1G), to an atypical polymicrogyria-like cortical malformation with cerebellar hypoplasia (figure 1F). This malformation consists of a moderately thick cortex (usually 7–10 mm), variable appearance of the cortical surface and boundary between cortical and white matter that appears smooth in some areas and pebbled in others, sparse or absent intracortical microsulci typical of polymicrogyria, and a paucity of deep gyral infolding.[55]

Clinical features

Most children with mutations of tubulin genes have severe intellectual disability and intractable seizures. The phenotype resembles classic lissencephaly, but can be more or less severe. However, too few affected individuals and details about their phenotype have been reported to define the range of abnormalities.

Syndromes, genetics, and molecular basis

By definition, tubulinopathies are always genetic. Investigators have identified nine genes (*DYNC1H1, KIF2A, KIF5C, TUBA1A, TUBA8, TUBB, TUBB2B, TUBB3, and TUBG1*; tables 3, 4), but we expect additional genes to be reported in the near future. Findings from functional studies suggest that abnormal brain development in tubulinopathies results from a dominant negative effect of heterozygous missense mutations (in the absence of loss-of-function mutations) on the regulation of microtubule-dependent mitotic processes in progenitor cells, and on the trafficking activities of the microtubule-dependent molecular

motors *KIF2A*, *KIF5C*, and *DYNC1H1* in postmitotic neuronal cells.[8] The appendix shows the range of imaging phenotypes associated with these mutations. The most severe end of the range includes lissencephaly with cerebellar hypoplasia groups c, d, and f in our earlier classification,[93] and consists of severe lissencephaly grade 1, agenesis of the corpus callosum, and very severe brainstem and cerebellar hypoplasia,[70] an imaging pattern that matches the two-layered form of lissencephaly. This form has been associated with mutations in *TUBA1A* and *TUBB2B*.[55] The next phenotype consists of moderate lissencephaly with cerebellar hypoplasia with lissencephaly grade 4 (pachygyria) that can appear mildly asymmetrical, with variable callosal defects and moderate hypoplasia of the brainstem and cerebellum (appendix).[70,94] The third phenotype has isolated lissencephaly sequence with posterior predominant lissencephaly matching the *LIS1* pattern (gradient with posterior more severe than anterior; appendix).[8,67,70]

The fourth group includes children described as having polymicrogyria rather than lissencephaly, plus variable agenesis of the corpus callosum and constant hypoplasia of the brainstem and cerebellum. Although the cortical malformation resembles polymicrogyria, these patients have atypical features. Some patients have hypoplasia of the brainstem and cerebellum with mildly simplified gyral pattern.[70]

Mutations in two genes that function in early development of the dorsal (ie, pallial) cerebrum have been associated with a polymicrogyria-like cortical dysplasia that resembles the tubulinopathies: *PAX6*, especially in rare patients with homozygous mutations, and *EOMES*.[87,95,98]

Lissencephaly and subcortical band heterotopia

Lissencephaly or smooth brain and the associated malformation known as subcortical band heterotopia are the classic malformations associated with deficient neuronal migration.[96] Lissencephaly is characterised by absent or abnormally wide gyri plus an abnormally thick cortex. Subcortical band heterotopia consists of a normal or mildly simplified gyral pattern combined with a smooth band of grey matter in the superficial and middle portions of the white matter. On the basis of findings from genetic studies, the full range of lissencephaly now extends from severe lissencephaly with cerebellar hypoplasia to classic lissencephaly to subcortical band heterotopia, and also includes a polymicrogyria-like cortical malformation that can be distinguished from both lissencephaly and typical polymicrogyria by high-resolution brain imaging (table 3).

Pathological changes

Several different types of lissencephaly have been recognised on the basis of pathological features. They are most readily distinguished on the basis of the number of cortical layers affected, and include two-layered, three-layered, and four-layered forms.[97] In the most common four-layered or classic form, the cortex is 12–20 mm thick and composed of a normal marginal layer, a superficial cellular layer that corresponds to the cortical plate, a cell sparse zone, and a deep cellular layer composed of heterotopic neurons. The rare two-layered form consisting of severe lissencephaly, frequent agenesis of the corpus callosum,

and severe brainstem and cerebellar hypoplasia occurs with tubulinopathies, although the causative genes are not known for more than half of cases.[57,70,97]

Subcortical band heterotopia consists of a normal six-layered cortex; a thin zone of white matter underlying the cortex, and a zone of dense heterotopic neurons that breaks up into nodules at the lower border, closely resembling the X-linked form of lissencephaly.[97] Classic four-layered lissencephaly and subcortical band heterotopia comprise a single malformation range on the basis of reports of rare patients with areas of lissencephaly that merge into subcortical band heterotopia, and families with lissencephaly in boys and subcortical band heterotopia in girls and women.[99,100]

Brain imaging

For all forms of lissencephaly, the brain surface appears smooth with areas of absent (agyria) and abnormally wide (pachygyria) gyri (figure 1E, 1G). The cerebral cortex is abnormally thick – 8–15 mm compared with 2.5–4 mm for normal cortex – except when the cerebral wall is thin, as can occur with two-layered and occasionally four-layered lissencephaly. Subcortical band heterotopia represents a forme fruste of lissencephaly in which the brain surface appears normal, except for shallow sulci (figure 1H). Just beneath the cortex, often separated from it by a few mm of white matter, lies a smooth band of misplaced neurons. Thick bands (5–10 mm) occur in the subcortical white matter beneath the deepest sulci, whereas thin bands can follow the cortex up into a gyrus.[17]

The severity of lissencephaly and subcortical band heterotopia varies from complete or nearly complete agyria (grades 1 and 2), to mixed agyria-pachygyria (grade 3), to pachygyria only (grade 4), to mixed pachygyria-subcortical band heterotopia (grade 5), and finally to subcortical band heterotopia only (grade 6).[96] The anterior to posterior gradient, sex distribution, and associated malformations are essential for recognition of the different genetic forms. Mutations of *DCX*, *ACTB*, and *ACTG1* result in a gradient with anterior more severe than posterior, whereas mutations of *LIS1*, *TUBA1A*, *TUBG1*, *DYNC1H1*, and other genes produce a gradient with posterior more severe than anterior.[8,55,64,96] Severe lissencephaly with agenesis of the corpus callosum in boys is strongly suggestive of *ARX* mutations. The most severe mutations result in a completely smooth brain surface with no apparent gradient.[60,96]

Clinical features

Children with the most common types of lissencephaly or subcortical band heterotopia typically seem normal as newborn babies. Most patients come to medical attention during their first year because of poor feeding, hypotonia, and abnormal arching or opisthotonus in newborn babies; delayed motor milestones later in the first year of life; or onset of seizures, which is the most common sign. The major medical problems encountered are ongoing feeding problems and gastro-oesophageal reflux, epilepsy of many different types that is often intractable, and recurrent aspiration and pneumonia due to feeding problems.

Between 35% and 85% of children with classic lissencephaly develop infantile spasms, often without classic hypsarrhythmia. The frequency of spasms is much lower in children with subcortical band heterotopia than in those with lissencephaly, but both groups of patients go

on to have mixed seizure types including focal, tonic, tonic-clonic, and atypical absence seizures. The frequency and severity vary greatly, but seizures are often difficult to control. Many patients have the classic electroclinical signs of Lennox-Gastaut syndrome, with intractable tonic seizures, atypical absences, and slow spike and wave discharges.[52] Among individuals with less severe developmental disabilities, cognitive development can slow after onset of seizures. Neurological outcome usually relates to lissencephaly grade or thickness of subcortical band heterotopia.[17]

Survival

Children with some lissencephaly syndromes (especially Miller-Dieker syndrome with deletions in 17p13.3, and severe forms of lissencephaly with cerebellar hypoplasia or the X-linked syndrome of lissencephaly with abnormal genitalia due to *ARX* gene mutations) have a severe course and high mortality rates. However, these data do not apply to children with less severe forms of lissencephaly, subcortical band heterotopia, or the *RELN*-associated type of lissencephaly with cerebellar hypoplasia, because all of these disorders are associated with better motor and cognitive function and longer survival.[96]

Syndromes, genetics, and molecular basis

Lissencephaly, subcortical band heterotopia, and lissencephaly with cerebellar hypoplasia are always genetic. Studies to date have identified 12 lissencephaly genes (table 3), which account for roughly 90% of patients.[8,56,59,61,65,68,71,101] However, several of these genes are associated with one or more specific lissencephaly or subcortical band heterotopia syndromes with different presentations. Although deletions and mutations in *LIS1* are the most common cause of lissencephaly, the contributions of these genes have been derived from separate studies over many years, making comparisons difficult.

The range of malformations associated with classic four-layered lissencephaly includes Miller-Dieker syndrome and isolated lissencephaly sequence, and extends to include subcortical band heterotopia, because a few affected individuals have both lissencephaly and subcortical band heterotopia. Miller-Dieker syndrome is a syndrome of several congenital anomalies, characterized by severe four-layered lissencephaly with diffuse agyria and no clear gradient, typical facial appearance, and other birth defects (eg, heart malformations).[69] The facial features include prominent forehead, bitemporal hollowing, short nose with upturned nares, protuberant upper lip with thin vermilion border, and small jaw. All patients with Miller-Dieker syndrome have large deletions in chromo some 17p13.3 that include *LIS1*, *YWHAE*, and all intervening genes.[69]

Isolated lissencephaly sequence (the most common lissencephaly syndrome) consists of classic four-layered lissencephaly, normal or slightly small cerebellum, and normal facial appearance except for mild bitemporal hollowing and small jaw.[102] Different patterns of lissencephaly have been reported with mutations of the known causative genes. Boys with *DCX* mutations have either severe lissencephaly with diffuse agyria or frontal predominant lissencephaly. Children with *LIS1* deletions or other mutations have posterior predominant lissencephaly, most often with frontal pachygyria and posterior agyria (grade 3). An identical pattern occurs in children with mutations in *TUBA1A* codon Arg402.[70]

Subcortical band heterotopia is only rarely associated with other congenital anomalies. Most patients are female, because the most common cause is heterozygous mutations of the *DCX* gene.[105] However, affected boys have also been reported.[103,104] Subcortical band heterotopia associated with mutations of *DCX* is characterised by diffuse thick bands with no apparent gradient, or by frontal thin bands.[29,106] Subcortical band heterotopia associated with mutations or deletions in *LIS1* is characterised by partial posterior thin or intermediate bands with an obvious gradient, with posterior more severe than anterior heterotopia. This genotype is a rare cause of subcortical band heterotopia, and some patients have mosaic mutations in *LIS1*[28,30] or mosaic deletions in 17p13.3 (including *LIS1*).[96]

Lissencephaly with cerebellar hypoplasia was previously described as a heterogeneous range of malformations, but is now sorted into two major subtypes. The first – lissencephaly with cerebellar hypoplasia group b in an earlier classification[93] – consists of mild frontal predominant lissencephaly, plus severe hippocampal and cerebellar hypoplasia and dysplasia. This pattern has been associated with mutations in *RELN* or *VLDLR* (an essential cell-surface receptor for reelin). Thus, this group is designated as reelinopathies.[61,62,101,107] The second consists of more severe lissencephaly with cerebellar hypoplasia, as occurs in the tubulinopathy range.[55,70] The rare Baraitser-Winter syndrome and X-linked syndrome of lissencephaly with abnormal genitalia are not discussed in this Review.[60,64]

Polymicrogyria with or without schizencephaly

The term polymicrogyria describes a cerebral cortex with many excessively small convolutions, which might or might not be visible on gross inspection of the brain surface.[108] One specific pattern of polymicrogyria occurs in schizencephaly, and indeed several of the initial descriptions of polymicrogyria are derived from brains with schizencephaly.[109,110] As part of the definition of schizencephaly, the clefts need to be lined by polymicrogyria. The pathogenesis of polymicrogyria is not understood and is probably variable in relation to its remarkable causal heterogeneity.

Pathological changes

Macroscopically, polymicrogyria appears as an irregular or pebbled cortical surface. The distribution varies greatly from bilateral symmetrical to asymmetrical to unilateral forms. The perisylvian cortex is the most frequently affected. The cortex often appears thickened to 8–12 mm, but when viewed microscopically is overfolded and not necessarily thick. Microscopically, polymicrogyria can show several different architectural patterns, although all result from abnormal development or loss of neurons in middle and deep cortical layers, variably associated with an unlayered cortical lamination, excessive folding, and fusion of adjacent gyri.[111] The extent of polymicrogyria seen microscopically might be greater than that suggested by macroscopic inspection.[19]

When schizencephaly is present, the cortex edges can seem to fuse (closed lips) or stay at distance (open lips). The clefts of schizencephaly can be unilateral or bilateral. An area of polymicrogyria can occur in the cortex contralateral to a unilateral cleft. The cortex surrounding the cleft shows loss of laminar architecture, forming irregular heterotopic aggregates of grey matter that can be displaced into the depth of the lesion, whereas the

ventricular wall is displaced upward, resulting in a seam where ependymal and malformed grey matter are adjacent.[109–111]

Although the term polymicrogyria as most often descriptively used in neuroimaging does not require specific histological abnormalities, neuropathologists use it to describe an abnormality of excessive gyration and a microscopic abnormality of cortical structure and lamination. In our view, such a loose definition of polymicrogyria has led to substantial confusion for both clinical care and research. Emerging data from both genetics and mouse models[4,5,45,56–58] indeed show different pathogenesis for the heterogeneous group of cortical malformations all now designated as polymicrogyria, and will presumably lead to reorganisation of taxonomy in the near future.

Brain imaging

Because brain-imaging studies done with low-field strength MRI do not show microgyri well, polymicrogyria is frequently misdiagnosed as pachygyria. With use of high-field strength MRI with appropriate age-specific protocols, polymicrogyria can be reliably differentiated – especially the classic form of polymicrogyria with perisylvian location (figure 1N), schizencephaly (figure 1M), and several other forms – from other cortical malformations. In some circumstances, special techniques (eg, inversion recovery, volume averaging, focal coils, and curvilinear reformatting) might be needed.[45] Ultra-high-field MRI (7T) can show polymicrogyria in brain areas where the cortex appears normal at lower field strengths and properly show the actual morphological extent of the malformation (figures 1N, 2).

Polymicrogyric cortices often appear mildly thickened (usually 6–10 mm) because of cortical overfolding (figure 2). In young children with polymicrogyria, the cortex might not appear particularly thickened because of the immature state of myelination.[112] T2 signal within the cortex is usually normal. Diffusely abnormal signal in white matter should suggest in-utero infection (eg, by cytomegalovirus), peroxisomal disorders (figure 1L), or several rare polymicrogyria or polymicrogyria-like syndromes.[83,113] For example, most patients with cobblestone malformations (figure 1I, 1J, 1K; appendix) – which were once classified as polymicrogyria – have abnormal white-matter signals in infancy.

In schizencephaly, the grey matter lining the cleft has the imaging appearance of polymicrogyria with an irregular surface, deep infolding (the cleft), mildly thick cortex, and stippling of the interface between grey and white matter (figure 1M). Schizencephaly is often bilateral but frequently asymmetrical; the contralateral hemisphere should be closely assessed for milder clefts or polymicrogyria without cleft.[114]

Polymicrogyria has been described in several topographic patterns.[20] The most common by far is bilateral perisylvian polymicrogyria (figure 1N), which varies from the posterior perisylvian region only (grade 4), to the entire perisylvian region (grade 3), to the perisylvian region with extension to other brain regions but not the poles (grade 2), to most of the brain including either or both the frontal or occipital poles (grade 1). However, the perisylvian regions are always the most severely affected. Furthermore, perisylvian polymicrogyria can be bilateral symmetrical, bilateral asymmetrical, or unilateral. Other

patterns are almost always bilateral and symmetrical, and include generalised, frontal, posterior (probably), mesial parieto-occipital, and rare diffuse parasagittal polymicrogyria.[21,22,115] Polymicrogyria also occurs in overlying periventricular nodular heterotopia.[116]

Clinical features

The clinical manifestations of polymicrogyria vary widely, and depend on several factors. The most severe outcomes occur in children with severe microcephaly (−3 SD or smaller), abnormal neurological examination (especially spasticity), widespread distribution of polymicrogyria, and additional brain malformations (especially cerebellar hypoplasia). The best outcomes are in individuals who have localised unilateral polymicrogyria without other malformations. Polymicrogyria can affect eloquent cortical areas representing language or primary motor functions, yet these functions can be retained with little or no disability.[117]

Bilateral perisylvian polymicrogyria with oromotor dysfunction (congenital suprabulbar palsy), intellectual disability, and epilepsy were described as the congenital bilateral perisylvian syndrome.[23,24] A small group of patients have unilateral perisylvian polymicrogyria and present with mild hemiparesis or seizures. Although their developmental and neurological deficits are typically less severe than those of patients with bilateral disease, they can develop intractable seizures and epilepsy with continuous spikes and waves during sleep.[25] Patients with closed-lip unilateral schizencephaly typically present with hemiparesis or motor delay, whereas patients with open-lip schizencephaly typically present with hydrocephalus or seizures.[118] Outcomes are worst for patients with bilateral open-lip schizencephaly and best for those with unilateral closed-lip schizencephaly.[114]

Syndromes, genetics, and molecular basis

Summarising the causes of polymicrogyria is difficult because of the different pathological forms, very different distributions, evidence of extrinsic (ie, non-genetic) causes, and sometimes loose use of the term. The substantial pathological, imaging, and clinical heterogeneity suggest that polymicrogyria is not a single malformation *per se*, but can be grouped by diverse phenotypes.

First are phenotypes with known or presumed vascular or infectious causes. Several of the earliest descriptions of polymicrogyria came from studies of schizencephaly,[119,120] which is associated with extrinsic causes such as vascular insufficiency (especially during twin pregnancies) and cytomegalovirus infections.[83] Both of these causes can result in polymicrogyria without clefts. Reports linking mutations of *EMX2* with schizencephaly[121,122] have never been confirmed. Our experience suggests that cytomegalovirus might be a comparatively common cause of polymicrogyria.

Some copy-number variants have been associated with polymicrogyria (table 4), but only deletions in 1p36.3 and 22q11.2 are common.[90,92] Indeed, when these two loci are excluded, copy number variants seem to be rare. The causal gene has not been identified for any of these loci.

All types of single-gene inheritance have been reported for polymicrogyria, including several families with autosomal dominant inheritance[123,124] and some families with rare autosomal recessive forms.[121,123,125,126] Several reports have described X-linked forms, although the lack of substantiation of these findings makes us skeptical of the role of these loci in polymicrogyria.[123,127–129]

Several syndromes with diffuse or bilateral frontal predominant polymicrogyria have been described (eg, the Warburg Micro syndrome; table 4). Pathological changes have not been defined for most of these disorders, and whether these syndromes are true polymicrogyria or polymicrogyria-like cortical malformations is usually not clear. Polymicrogyria-like cortical malformations have been reported with several metabolic diseases with severe phenotypes, including Zellweger syndrome,[130,131] neonatal adreno leukodystrophy,[113] fumaric aciduria,[75] mitochondrial diseases,[132] glutaric aciduria type 2,[133] maple-syrup-urine disease,[134] and histidinaemia.[135] However, the histopathology differs from classic polymicrogyria for several of these disorders, especially the peroxisomal disorders and glutaric aciduria type 2.

Periventricular nodular heterotopia

Periventricular nodular heterotopia is the most frequent form of neuronal heterotopia, which is defined as groups of normal neurons in an inappropriate location. Other major types include subcortical nodular heterotopia and leptomeningeal (marginal) glioneuronal heterotopia. Periventricular nodular heterotopia, however, is the only type for which genetic and clinical associations have been extensively studied. Anatomically, periventricular nodular heterotopia consists of nodular masses of grey matter that line the ventricular walls and protrude into the lumen, resulting in an irregular outline (figure 1P). It is a fairly common malformation that can occur as a single nodule, or as many contiguous or non-contiguous nodules. When the nodules are bilateral and numerous, a genetic basis is probable and other brain malformations are often reported.[18,116,136]

Pathological changes

Microscopically, the heterotopic tissue contains both neurons and glial cells, and forms clusters of rounded, irregular nodules separated by layers of myelinated fibres.[137] Individual nodules, or heterotopion, can lack any organisation or have rudimentary lamination.

Brain imaging

Patients with the classic X-linked form (figure 1P) typically have bilateral contiguous periventricular nodular heterotopia that spares the temporal horns, and mild cerebellar vermis hypoplasia with mega-cisterna magna.[18,99] Patients with rare autosomal recessive bilateral periventricular nodular heterotopia can have severe congenital microcephaly and thin overlying cortex with abnormal gyri.[138] In the fairly common posterior predominant syndromes, the periventricular nodular heterotopia is limited to the trigons, temporal, and occipital horns, and can be associated with overlying polymicrogyria (figure 1O), hippocampal and cerebellar hypoplasia, or hydrocephalus.[116,136]

Clinical features

The clinical presentation and course in patients with periventricular nodular heterotopia varies greatly among the recognised syndromes (table 5). In individuals with periventricular nodular heterotopia, but no other brain malformations, seizures and learning problems are common, whereas more severe developmental problems are uncommon but can occur. When microcephaly or other brain malformations are diagnosed, the likelihood of cognitive impairment increases greatly. Among all forms of periventricular nodular heterotopia, the most common and often the presenting problem is epilepsy, which has been reported in 80–90% of patients. The age at seizure onset is variable. Most patients have focal seizures, which can be easily controlled or refractory.[18] Findings from studies using depth electrodes showed that the nodules are intrinsically epileptogenic, and often participate in complex epileptogenic networks, making surgical treatment of epilepsy particularly difficult.[144]

Syndromes, genetics, and molecular basis

The most common form of diffuse periventricular nodular heterotopia and the linked Ehlers-Danlos form are caused by mutations in the X–linked *FLNA* gene.[18] This syndrome predominately affects girls, and several large pedigrees suggest increased prenatal lethality of affected boys.[145] Affected girls, with rare exceptions, have normal intelligence, but might have learning problems. The phenotype in boys is much more variable, ranging from prenatal lethality to the mild female phenotype. However, cognitive impairment is more common than in females.[27,139] In a large study of 120 patients with periventricular nodular heterotopia, *FLNA* mutations were found in 10 of 10 families with X-linked inheritance.[18] Overall, mutations were reported in 49% of individuals with classic bilateral periventricular nodular heterotopia, irrespective of familial or sporadic occurrence. The sex ratio was skewed with 93% of mutations in females and 7% in males.

A rare autosomal recessive form associated with severe congenital microcephaly and diffuse bilateral periventricular nodular heterotopia has been reported in two families.[138] The affected children had severe developmental handicaps. Other genetic forms of periventricular nodular heterotopia have been mapped to chromosomes 5p15, 5q14.3, 6p25, 6q27 and 7q11[23] (table 5),[140–143,146] but a putative causal gene has only been identified for the 6q27-related form.[91]

The two genes associated with periventricular nodular heterotopia (*ARFGEF2* and *FLNA*) regulate actin binding, vesicle trafficking, cell adhesion, and function of radial glia;[138,147] mutations of these genes cause abnormalities of the ventricular epithelium or neuroependyma.[148] *FLNA* encodes a large actin-binding phosphoprotein that stabilises the cytoskeleton andcontributes to formation of focal adhesions along the ventricular epithelium.[149,150] *ARFGEF2* encodes a protein that phosphorylates guanine diphosphate. Guanine triphsophate activates ADP-ribosylation factors, which regulate vesicle trafficking and transport of molecules from the cell interior to cell surface for binding to other molecules or cell secretion. Thus, this protein might assist in the transport of FLNA to the cell surface.

Conclusions and future directions

The highly variable clinical presentations and burden of disability associated with MCD result from diversity in pathophysiological disruption of brain development and the consequent anatomical and functional brain impairment. Understanding of the genetic and molecular basis of cortical development is advancing rapidly, with new genes and new roles for known genes being reported, providing evidence that many cortical malformations are probably secondary to abnormalities occurring at several interdependent developmental stages. Findings from studies of human brain tissue samples that are made available after surgical resection for intractable epilepsy show that postzygotic mutations affecting a subset of neural cells can cause abnormal development and migration, changing the perception of genetic MCD as disorders affecting the whole brain. At the same time, findings from different experimental models are revealing the diversity underlying epileptogenesis in MCD, and might help to pave the way for innovative treatment strategies. For example, findings from an Arx((GCG)7/Y) knock-in mouse model showed normal development of GABAergic neurons, with normal migrations of pyramidal cells and cortical layering, but a substantial increase in the frequency of excitatory inputs associated with a remodelling of axonal arborisation of hippocampal pyramidal neurons, suggesting that epilepsy results from remodelling of the glutamate network and that secondary changes are essential for the development of disease-specific phenotypes.[151] In-utero silencing of the *Srpx2* gene or increased acetylation of a-tubulin causes a neuronal migration phenotype with postnatal spontaneous epileptiform activity, which can be prevented by maternal administration of the tubulin deacetylase inhibitor tubacin.[152] This model provides an example of a drug based strategy to prevent epileptiform manifestations of developmental origin. Patch-clamp recordings from dysplastic neurons in acute slices of brains from patients with FCD type 2b show excitatory responses of GABA(A) receptors that are substantially attenuated by the SLC12A2 inhibitor bumetanide,[153] a finding that could account for resistance of seizure activity in FCD to anticonvulsants that increase GABAergic function, and might justify add-on trials with bumetanide. These examples clearly show that addressing the diversity of mechanisms causing MCD and their secondary changes could lead to rational, targeted treatment options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms “focal cortical dysplasia”, “hemimegalencephaly”, “heterotopia”, “lissencephaly”, “malformations of cortical development”, “megalencephaly”, “pachygyria”, “polymicrogyria”, and “subcortical band heterotopia”, from 1990 until July, 2013 and through quotation of classical genetic and neuropathological work. Articles were also identified through searches of the authors’ own files. With a few exceptions concerning seminal neuropathological descriptions, only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

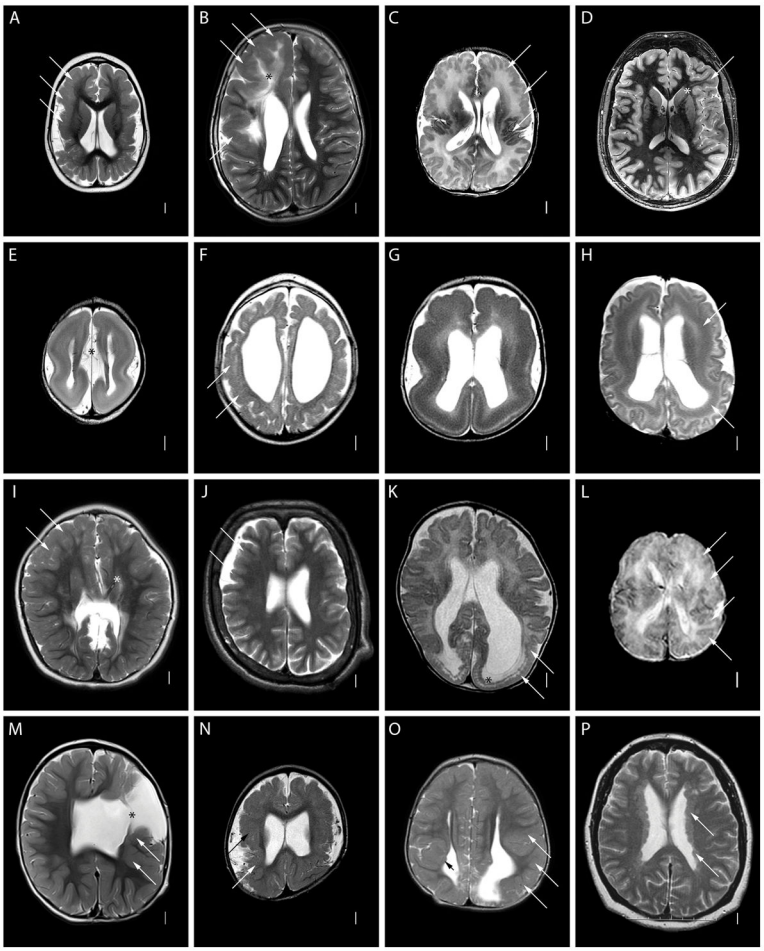

Figure 1.

Axial T2-weighted images at the level of the mid-lateral ventricles showing different malformations of cortical development. Long arrows show representative areas of cortical malformation (A–D, F, I–O), subcortical band heterotopia (H) or periventricular nodular heterotopia (P). The short black arrow shows a small periventricular nodular heterotopia (O). Asterisks denote abnormal white matter (B), focal transmantle dysplasia (D), wide inter hemispheric space due to absent corpus callosum (E), a shunt (I), and an open-lip cleft (M). The malformations of cortical development shown include severe congenital microcephaly with a PMG-like cortical malformation (A), right-sided dysplastic megalencephaly (hemimegalencephaly) (B), megalencephaly and frontal-perisylvian polymicrogyria (C), focal cortical dysplasia type 2b (D), severe lissencephaly with cerebellar hypoplasia and absent corpus callosum (E), PMG-like cortical malformation in a tubulinopathy (F), grade 3 classic lissencephaly (G), diffuse subcortical band heterotopia in a female (H), frontal predominant cobblestone malformation in muscle-eye-brain disease (I), frontal predominant cobblestone malformation in autosomal recessive cutis lax (J), posterior predominant cobblestone mutation in a child with congenital muscular dystrophy (K), peroxisomal cortical malformation in Zellweger syndrome (L), classic schizencephaly with a left frontal open-lip cleft (M), perisylvian polymicrogyria imaged at 7 Tesla (N), posterior periventricular nodular heterotopia with overlying PMG (O), and bilateral diffuse

periventricular nodular heterotopia (P).(This is a short form, see Supplementary Text for longer version).

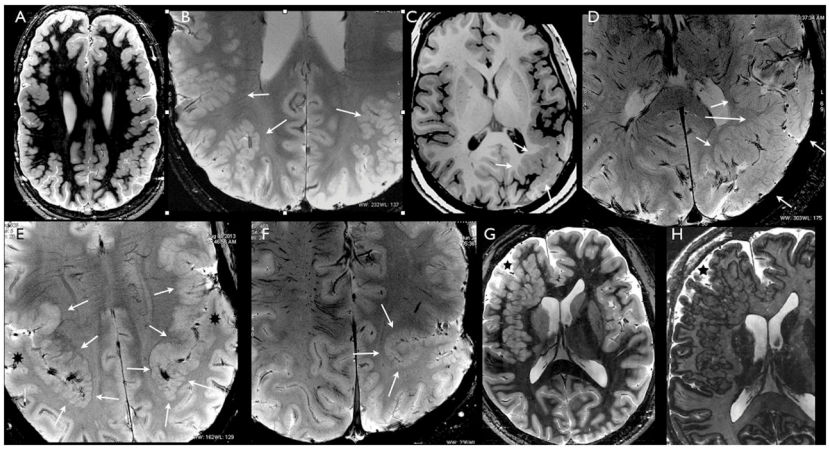

Figure 2.

Axial MRI images at 7T showing different morphological aspects of polymicrogyria in five young adult patients. Images ‘A’ and ‘G’ are inversion recovery (IR) weighed (W), image ‘C’ is T1W, images ‘B’, ‘D–F’ are susceptibility (S) W images; image ‘H’ shows a detail of image ‘G’ and is obtained using the tissue border enhancement by IR acquisition technique.[174] ‘A’ shows the pebbled aspects of the grey matter typical of polymicrogyria, with areas of thickening and infoldings, involving the posterior frontal and parietal cortex on both sides, in a young woman. ‘B’, is taken from the same patient as ‘A’, using SW sequences. Detail of the cortex at the parietal lobe level, discloses the underlying structure of the malformed cortex, which is thin and overfolded, with ribbon like aspect. The arrows indicate the areas where these characteristics are more prominent. Note that the cortex has normal thickness and shape in the mesial hemispheric surface. ‘C’ shows gross thickening and abnormal sulcation of the posterior perisylvian and parietal cortex of the left hemisphere in a young adult man. ‘D’, showing a detail of ‘C’ obtained using SW sequences, discloses ribbon like cortical overfolding bordering the abnormal sulci. For comparison, see the normal cortex in the contralateral hemisphere. ‘E’ is obtained using SW in the same patient as in figure 1N. Note the abrupt transition between the abnormally thick and overfolded cortex in the perisylvian borders (arrows) and the normal temporo-parietal cortex (black asterisks). ‘F’ shows abnormal infolding due to abnormal sulcation and cortical thickness in a young man with left unilateral perisylvian polymicrogyria. ‘G’ shows an extensive area of heterotopia involving most of the right frontal lobe in a young man. The macronodular aspect of the heterotopia and the irregular surface of the overlying cortex (black asterisk) make this malformation not easily distinguishable from what is seen, for example, in the left parietal lobe in patients shown in ‘A’ and ‘C’. Tissue border enhancement, used in ‘H’ (showing a detail of ‘G’), helped defining the grey-white matter border and diagnose this malformation as heterotopia even if the overlying cortex contains small gyri and abnormal sulci.

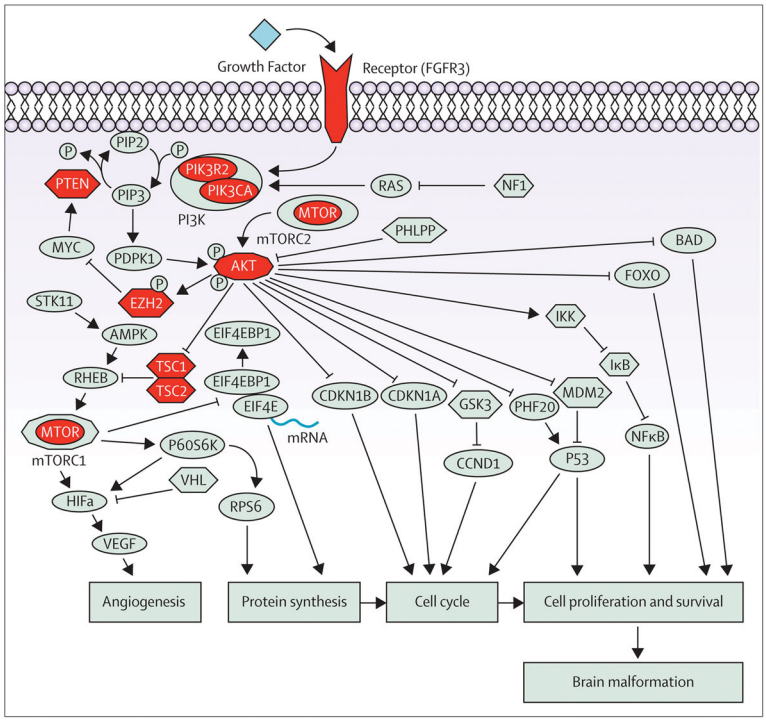

Figure 3.

Schematic representation of the PI3K-AKT-mTOR signaling pathway. Genes encoding proteins with activator effects on the downstream signaling components are represented by ellipsis, genes encoding proteins with inhibitory effect are represented by hexagons and AKT gene family and MTORC1, which may have both activating and repressor effect, are represented by decagons. Genes encoding proteins of the PI3K-AKT-MTOR pathway already implicated in malformations of cortical development in human disease are coloured in red. Protein abbreviations are provided in the appendix.

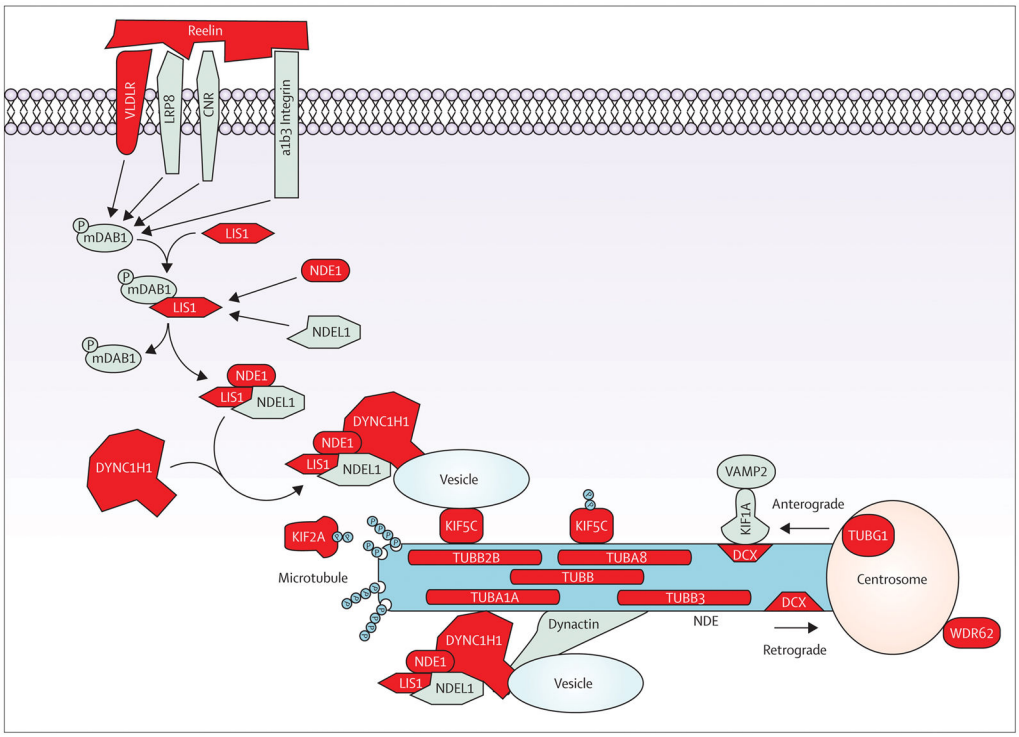

Figure 4.

Reelin-LIS1-tubulins pathway. Schematic representation of the reelin-mediated signaling pathway for neuronal migration. Reelin binding to one of three receptors complexes (CNR, VLDLR/LRP8, or β-integrin) activates mDAB, which mediates the binding of LIS1 with NDE1/NDE1L and DYNC1H1. The interaction of the LIS1-NDE1/NDE1L-DYNC1H1 complex with KIF5C mediates the anterograde transport, whereas its interaction with dynactin mediates the retrograde transport. KIF1A mediates the VAMP2 transport through the interaction with DCX, and KIF2A mediates microtubule depolymerisation. Genes encoding proteins of the reelin-LIS1-tubulins pathway already implicated in malformation of cortical development in human disease are coloured in red. Protein abbreviations are provided in the appendix.

Table 1

Presenting signs and predictors for prognosis in MCD

Neurologic symptoms	Severity		
	Most severe	**Intermediate**	**Least severe**
Head size (OFC)	Microcephaly (<−3 SD)	Megalencephaly (>+3)	Normal head size
Tone	Spasticity	Hypotonia	Normal tone
Seizure onset	Early (0–3 months)	Infancy (3–12 months)	Later (after 1 year)
Seizure type	EIEE-ISS-LGS-myoclonic	Nonspecific generalized	Focal, other types
MCD distribution	Diffuse	Frontal-perisylvian	Posterior or other
MCD symmetry	Bilateral symmetric	Bilateral asymmetric	Unilateral

Abbreviations: EIEE, early infantile epileptic encephalopathy; ISS, infantile spasms; LGS, Lennox-Gastaut syndrome; MCD, malformations of cortical development; OFC, occipito-frontal circumference; SD, standard deviations.

Table 2

Genes and phenotypes for megalencephaly and dysplastic megalencephaly

Gene	Cytogenetic location	Phenotypes
Megalencephaly-polymicrogyria and dysplastic megalencephaly		
AKT3	1q43q44	MPPH, DMEG[12,13,26]
EZH2	7q36.1	Weaver syndrome[32–34]
FGFR3	4p16.3	Thanatophoric dysplasia[35,36]
PIK3CA	3q26.32	MCAP, CLOVES[12,26,37]
PIK3R2	19p13.11	MPPH[26]
Focal cortical dysplasia		
PTEN	10q23.31	FCD, BRRS, CD[38]

Key: Cyto; cytogenetic location; BRRS, Bannayan-Riley-Ruvalcaba syndrome; CD, Cowden disease; DMEG, dysplastic MEG; FCD; focal cortical dysplasia; MCAP, megalencephaly-capillary malformation syndrome; MEG, megalencephaly; MPPH, megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome.

Table 3

Genes and phenotypes associated with lissencephaly, subcortical band heterotopia, and polymicrogyria-like malformations

Gene	Cytogenetic location	Phenotypes
LIS 3 layer with ACC		
ARX	Xp22.1	XLAG[59,60]
LIS Reelin type with a>p gradient		
RELN	7q22.1	LCH, Reelin-type[61,62]
VLDLR	9p24.2	LCH, Reelin-type[63]
LIS 2 and 4 layer with a>p gradient		
ACTB	7p22.1	BWS LIS grade 4–5 a>p[64]
ACTG1	17q25.3	BWS LIS grade 4–5 a>p[64]
DCX females	Xq23	SBH[29,65]
DCX males	Xq23	ILS, LIS grades 1–4[45,66]
LIS 2 and 4 layer with p>a gradient		
DYNC1H1	14q32.31	ILS, LIS grade 4[8,67]
KIF2A	5q12.1	ILS, LIS grade 4[8]
LIS1	17p13.3	ILS, LIS grade 3–4[66,68]
Deletion *LIS1* and *YWHAE*	17p13.3	MDS, LIS grade 1–2[69]
TUBA1A	12q13.12	ILS, LIS grade3; LCH, LIS grade1–4; PMG-like[55,70,71]
TUBB2B	6p25.2	ILS, LIS grade3; LCH, LIS grade1–4; PMG-like[55,72]
TUBG1	17q21.2	ILS, LIS grade 3–4[8]

Key: BWS, Baraitser-Winter syndrome; Cyto; cytogenetic location; ILS, isolated lissencephaly sequence; LCH, lissencephaly with cerebellar hypoplasia; LIS, lissencephaly; MDS, Miller-Dieker syndrome; PMG, polymicrogyria; SBH, subcortical band heterotopia; XLAG, X-linked lissencephaly with abnormal genitalia. a>p, anterior more severe than posterior; p>a, posterior more severe than anterior.

* Full names for genes are provided in Supplementary Table 4.

Table 4

Associated genes, cyotogenetic rearrangements, and phenotypes in polymicrogyria

Gene	Cytogenetic location	Syndromes/Phenotypes
Severe congenital microcephaly with diffuse polymicrogyria or polymicrogyria-like MCD		
NDE1	16p13.11	MIC FBD BDP[73,74]
WDR62	19q13.12	MIC BDP[5–7]
Diffuse polymicrogyria plus other abnormalities		
FH	1q43	Fumaric aciduria[75]
KIAA1279	10q21.3	Goldberg-Shprintzen syndrome[76]
NSDHL	Xq28	CHIME-like syndrome[77]
OCLN	5q13.2	BLC, BFP[78]
Frontal polymicrogyria plus other abnormalities		
GPSM2	1p13.3	Chudley-McCullough syndrome[79]
RAB3GAP1	2q21.3	Micro syndrome, BDP[80]
RAB3GAP2	1q41	Micro syndrome, BDP[80]
RAB18	10p12.1	Micro syndrome, BDP[80]
Perisylvian polymicrogyria plus other abnormalities		
CHD7	8q12.2	CHARGE syndrome[79]
Polymicrogyria with other changes of cytomegalovirus		
CMV	n.a.	MIC-PMG-HHLL[83]
Tubulinopathies with polymicrogyria-like MCD (or lissencephaly)		
DYNC1H1	14q32.31	ACC, microcephaly, lissencephaly, PMGL[8]
KIF5C	2q23.1	ACC, microcephaly, lissencephaly, PMGL[8]
TUBA1A	12q13.12	ACC, CBLH, microcephaly, lissencephaly PMGL[55]
TUBA8	22q11	ACC, CBLH, microcephaly, PMGL[84]
TUBB2B	6p25.2	ACC, CBLH, microcephaly, lissencephaly, PMGL[55,56,72]
TUBB3	16q24.3	ACC, CBLH, microcephaly, PMGL[85]
TUBB	6p21.33	ACC, CBLH, microcephaly, PMGL[86]
Intermediate progenitor cell pathway defects with polymicrogyria-like MCD		
TBR2/EOMES	3p21	ACC, microcephaly, PMGL[87]
PAX6	11p13	Aniridia[88]
PAX6 homozygous	11p13	MOPH-ACC-BDP[89]
Copy number variants associated with polymicrogyria		
Deletion	1p36.3	BPP[90]
Duplication	2p13p23	BPP[90]
Deletion	4q21q22	CBLH BPP[90]
Deletion	6q26q27	ACC PNH BDP[90,91]
Deletion	13q3	BPP[90]

Gene	Cytogenetic location	Syndromes/Phenotypes
Deletion	18p11	BPP[90]
Deletion	21q2	BPP[90]
Deletion	22q11.2	DiGeorge syndrome[92]

Key: ACC, agenesis of the corpus callosum; BDP; bilateral diffuse PMG; BFP, bilateral frontal PMG; BLC, band-like calcifications (a.k.a. pseudoTORCH); CBLH, diffuse cerebellar hypoplasia; CMV, cytomegalovirus; Cyto, cytogentic location; FBD, fetal brain disruption; homozy, homozygous mutations; MIC, microcephaly; MCD, malformation of cortical development; MOPH, microphthalmia; PMG, polymicrogyria; PMGL, polymicrogyria-like; PNH, periventricular nodular heterotopia.

Table 5

Associated genes, cytogenetic rearrangements, and phenotypes in periventricular nodular heterotopia

Gene	Cytogenetic location	Phenotype
Microcephaly with periventricular nodular heterotopia		
ARFGEF2	20p13	MIC PNH diffuse[138]
Periventricular nodular heterotopia		
FLNA	Xq28	PNH diffuse[18,139,149]
Duplication	5p15.1	PNH anterior[140]
Duplication	5p15.33	PNH diffuse[140]
Deletion	5q14.3	PNH posterior[141]
Deletion	6p25	PNH scattered[142]
Deletion-C6orf70	6q27	PNH variable, PMG[91]
Deletion	7q11.23	PNH anterior, Williams syndrome[143]

PNH=periventricular nodular heterotopia. PMG=polymicrogyria.