Published in final edited form as:

Pediatr Clin North Am. 2015 June ; 62(3): 571–585. doi:10.1016/j.pcl.2015.03.002.

Genomic Variants and Variations in Malformations of Cortical Development

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Abstract

Malformations of cortical development (MCD) are a common cause of neurodevelopmental delay and epilepsy and are caused by disruptions in the normal development of the cerebral cortex. Advances in genetic tools have expanded our understanding of the genetics of these malformations over the past few years, with a number of new causative genes identified in patients with MCD. In addition, there has been a vast expansion in the phenotypic characterization of the known genes, with a wide range as well as severity of malformations being reported. There is increasing evidence of role of *de novo* mutations, including those occurring post fertilization, in MCD. These “somatic” mutations may not be detectable by traditional methods of genetic testing performed on blood DNA. Identification of the genetic etiology can help in guiding families in future pregnancies. Recent work has highlighted how elucidation of key molecular pathway can also allow for targeted therapeutic interventions.

Keywords

malformations of cortical development; genomic variants; somatic mutation; microcephaly; megalencephaly; cortical dysplasia; lissencephaly; polymicrogyria

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Disclosure: No conflicts of interest to declare

CLINICAL BACKGROUND

The development of the human cortex is a complex and tightly regulated process. During development, distinct cell types must proliferate, differentiate, migrate and integrate to form a highly complex structure, capable of complex cognition, language, and emotion¹. Disruptions in any of these processes lead to malformations of cortical development (MCD) which are common causes of neurodevelopmental delay and/or epilepsy². Individuals presenting early can show feeding difficulties soon after birth (in some instances, in utero swallowing difficulty may present as polyhydramnios), abnormal head size (micro- or macrocephaly), epileptic encephalopathies and/or global developmental delay. Some patients with MCD may present early with severe neurological impairment, while others present with epilepsy and mild functional impairment at a later age. Those individuals that present later may exhibit focal epilepsy, learning difficulty and behavioral issues, such as attention deficit hyperactivity disorder³. Occasionally, a few individuals may be diagnosed only on screening as their deficit may not be clinically apparent.

Classification systems for MCD, first introduced in 1996 and subsequently revised in 2001, 2005 and 2012 to incorporate the improved understanding of cortical development, divide MCD into three major groups- malformations secondary to abnormal neuronal and glial proliferation or apoptosis, malformations due to abnormal neuronal migration and malformations secondary to abnormal postmigrational development. This system is based on the developmental steps at which the process is first disrupted, the underlying genes and biological pathways affected and imaging features², though there is surprising overlap in the phenotypes of many genes, reflecting involvement of some genes in more than one stage of development.

Genomic variants are changes in one allele of a gene of an individual compared to a reference genome. Variants can be small (<1 kilobasepair) and include substitutions and small insertions and deletions (indels), or can be large (>1 kilobasepair) and include copy number variants (larger insertions or deletions), and rearrangements, such as translocation, and inversion. Lastly, genomic variants also include whole chromosome numerical alterations such as aneuploidy. While many variants are not associated with disease (and instead are referred to as benign variants) certain deleterious variants that alter the function of a gene may cause disease, representing disease-causing mutations. Human genetic diseases have been traditionally been thought to reflect either inherited or *de novo* (spontaneous) variants. These mutations are present in all the cells of the affected individual and can be detected in any cell of the body, including readily available peripheral blood, and are referred to as “germline”. Somatic mutation, on the other hand, is a post-zygotic mutational event which leads to an individual having two or more populations of cells with distinct genotypes, despite developing from a single fertilized egg^{4,5}; somatic mutations thus represent a subset of the larger category of *de novo* mutations.

In this review, we will focus on the recent advances in understanding the genetics of MCDs, including recent updates on role of somatic mutations in MCDs. Large scale sequencing projects have led to an exponential increase in our knowledge of the genes associated with MCDs and we will attempt to address some of these recent discoveries. It is important to

note that while most MCDs are caused by genomic variants, a proportion of MCDs (such as schizencephaly) are associated with non-genomic mechanisms and may be secondary to environmental causes.

EMBRYOLOGY OF CEREBRAL CORTICAL DEVELOPMENT

The normal human cortex is composed of six distinct histological layers. Its development begins from neuroepithelial progenitors lining the lateral ventricles that divide to expand the progenitor pool and then give rise to intermediate progenitors that subsequently divide and give rise to neurons. The neurons migrate from the proliferative ventricular zones toward the pial surface of the brain to form the layered cortex, where the connections between neurons form and mature^{1,6}.

The principal excitatory neurons of the cerebral cortex and hippocampus are derived from an embryonic neuroepithelium, with progenitor cells lining the ventricular surface deep in the brain. In animal models, inhibitory neurons that populate the cerebral cortex are formed outside the cortex in a second proliferative zone in the basal forebrain called the ganglionic eminence, which generates the basal ganglia. These neurons migrate large distances in non-radial direction before turning radially to enter the cortex⁷. There is recent evidence that human interneurons are formed by a similar mechanism⁸. Astrocytic glial cells arise from several sources, including progenitors that also generate principal neurons⁹, whereas oligodendrocytes arise in the basal forebrain that generates cells for the entire forebrain¹⁰.

RECENT ADVANCES IN GENETICS AND PATHOMECHANISM OF MCD

Overview

Historically, geneticists have relied on principles of Mendelian inheritance to identify genes, which when perturbed, lead to development of specific symptoms. Linkage analysis, homozygosity mapping, positional cloning and/or candidate gene sequencing have helped identify the genetic causes of many forms of MCDs¹¹⁻¹⁴. Studying individuals/ families with MCDs allows one to understand the critical components of normal brain development and function.

More recently, high throughput next generation sequencing (NGS) allows one to interrogate multiple regions of the genome at once to identify tens of thousands of genetic variants in an individual's genome¹⁵. These variants can then be filtered bioinformatically using certain criteria such as absence in control population, allele frequency, predicted pathogenicity and inheritance model to narrow down the candidate gene list to a few genes. With NGS, causal variants can be identified in a few weeks and this has led to a surge in the identification of novel genes as well as new alleles in known disease genes. With these recent advances in genetics, certain MCD-related genes, such as *WDR62* and *DYNC1H1* have been associated with a broad range of malformations, suggesting that some of these genes are implicated in many developmental stages that are functionally and genetically interdependent³.

Improved genomic tools have shed light on the role of *de novo* mutations in intellectual disability¹⁶. While traditionally, *de novo* mutations were considered to have developed in the egg or the sperm of the unaffected parents, there is increasing evidence of the role of

post zygotic (or somatic) *de novo* mutations in neurological disorders as well. As these mutations may be present in only a small proportion of the cells in the body, traditional methods of testing using leukocyte derived DNA have been shown to miss majority of these somatic mutations¹⁷. More importantly, some of these mutations may be present only in the affected tissue and testing of non-affected tissue, such as blood DNA, may not be informative¹⁷⁻¹⁹.

Microcephaly

Primary Microcephaly—Primary microcephaly (or microcephaly vera) is defined as the clinical finding of a head circumference less than 3 standard deviations (SD) below the age- and sex-related mean which is present at birth and is commonly associated with intellectual disability²⁰. Genes known to cause primary microcephaly affect pathways involving neurogenesis, resulting in decreased number of neurons and smaller brain size². These pathways include cell cycle progression and checkpoint regulation (*MCPH1*, *CENPJ*, *CDK5RAP2*²¹), centrosome duplication (*NDE1*²²), centrosome maturation (*CDK5RAP2*, *CENPJ*²¹), cell proliferation (*STIL*, *ASPM*^{23,24}), mitotic spindle formation (*WDR62*, *NDE1*^{25,26}) and DNA repair (*PKNP*, *PCNT*^{27,28}). Aberrations in these pathways highlight the important role of centrosome in neuronal proliferation. The centrosome is a key microtubule organizing center that helps maintain the cellular cytoskeleton and coordinate the segregation of duplicated chromosomes during cell division. Mutations in genes encoding centrosomal proteins, or proteins required for proper chromosomal segregation account for the largest number of genetic causes of microcephaly and may form a common pathway to regulate neuronal progenitor proliferation²⁰.

With the exception of *WDR62* (polymicrogyria, subcortical heterotopia)²⁵ and *ARFGEF2* (periventricular nodular heterotopia)²⁹, primary microcephaly genes do not produce obvious brain anomalies except for simplified gyral pattern and hypoplasia of the corpus callosum^{27,30,31}. No definable clinico-radiological characteristics have been identified that separate the different types of microcephaly caused by mutations in different stages of the cell cycle², suggesting that sequence panels of genes are an efficient diagnostic approach.

Postmigrational Microcephaly—In contrast to primary microcephaly, individuals whose head circumference are normal or slightly small (2 SD below mean) at birth, but develop severe microcephaly in the first 1-2 years are referred to as postmigrational microcephaly². In these individuals, brain growth slows during late gestation or early postnatal period after normal early development. Examples of these genes include *CASK* (associated with microcephaly with disproportionate cerebellar and brainstem hypoplasia)³², *MECP2* (Rett syndrome)³³, *UBE3A* (Angelman syndrome)³⁴; and proteins related to protein synthesis, including transfer RNA (tRNA) splicing endonuclease subunit genes such as *TSEN54*, *TSEN2*, and *TSEN34*, and aminoacyl-tRNA synthetases such as *RARS2*, and *SEPSECS* associated with pontocerebellar hypoplasias^{2,35}. More recently, mutations in *QARS*, a cytoplasmic aminoacyl-tRNA synthetase has been reported in individuals with progressive microcephaly, intractable seizures, diffuse atrophy of the cerebral cortex and cerebellar vermis and considerably mild atrophy of the cerebellar hemispheres³⁶. As the

disruption occurs late in cerebral development, these disorders may someday be good candidates for intervention once the molecular causes have been elucidated.

Overgrowth Related Disorders

Megalencephaly And Hemimegalencephaly—Megalencephaly with polymicrogyria is a sporadic overgrowth disorder associated with markedly enlarged brain size (head circumference above 3 SD), sometimes seen with developmental vascular anomalies, distal limb malformations (polydactyly and syndactyly) and mild connective tissue dysplasia when it is referred to as megalencephaly-capillary malformation-polymicrogyria (MCAP) syndrome³⁷. Hemimegalencephaly, on the other hand, refers to asymmetric brain enlargement that is typically isolated, although it has been reported in association with tuberous sclerosis, hypomelanosis of Ito and Proteus syndrome¹⁸.

Hemimegalencephaly is associated with dysmorphic immature neurons, neuronal heterotopia and cortical dyslamination^{18,19}.

Recently, exome sequencing and targeted deep sequencing have identified *de novo* germline and post zygotic (or somatic) point mutations in *AKT3*, *PIK3CA* and *PIK3R2* in individuals with MCAP syndrome and hemimegalencephaly^{18,19,38}. Somatic CNV increases of chromosome 1q involving *AKT3* have also been identified in individuals with hemimegalencephaly^{19,39}. Mutations in *PTEN* also lead to megalencephaly, autism and tumor predisposition⁴⁰. The PI3Ks are a family of signalling enzymes that regulate a wide range of cellular processes, including growth, proliferation, survival, migration, and brain development. *PTEN* is a tumor suppressor gene that antagonizes the PI3K signalling pathway, while AKT kinases are downstream effectors of PI3K signalling and have a critical role in growth regulation. Gain of function mutations or increased copy number of *AKT3* hyperactivates the mTOR pathway, causing increased cell growth, ribosome biogenesis and messenger RNA translation. The TSC genes encode negative regulators of mTOR, so that loss of these genes (in Tuberous sclerosis) also leads to hyper-activation of mTOR, leading to overgrowth of normal cells and production of abnormal cells in many organs³⁸.

Focal Cortical Dysplasia—Focal cortical dysplasias (FCDs) are a heterogeneous group of disorders that are characterized by abnormal cortical lamination and defects of neuronal migration, growth and differentiation involving one discrete cortical region, several lobes or even the entire hemisphere⁴¹. FCDs are the most common cause of medically refractory epilepsy in the pediatric population. The etiology is heterogeneous and can be genetic or environmental. FCDs are classified into three groups⁴²:

- FCD I: Presents with mild symptoms, often seen in adults and changes are typically seen in the temporal lobe. Evidence suggests that prenatal and perinatal insults including extreme prematurity, asphyxia, bleeding, stroke, hydrocephalus and shaking injury are commonly observed in patients with FCD I.
- FCD II: Clinical symptoms are more severe with onset typically in childhood. Radiological changes are seen outside the temporal lobe with predilection for the frontal lobes. Histological characteristics of FCD II are more homogenous across patients and recent evidence points towards genetic mutations that lead to perturbation of mTOR

pathway in the pathogenesis of FCD type IIb⁴³. Recently, patients with mutations in *DEPDC5*, which typically cause epilepsy without any imaging abnormality, have been reported with FCD suggesting a “second hit” phenomenon, analogous to TSC, with a somatic mutation in the other allele of *DEPDC5* or another gene in the mTOR pathway causing the malformations in these patients⁴⁴

- FCD III: This is associated with acquired pathology during early development such as hippocampal sclerosis, vascular malformations, epileptogenic tumor or injury secondary to head trauma, encephalitis or hypoxic ischemic injury. As seen in FCD IIb, dysregulation of mTOR pathway has been described in certain forms of FCD III⁴³.

Abnormal Neuronal Migration

Heterotopia—Heterotopia can range from periventricular nodular heterotopia (PVNH) (Figure 1A) to periventricular linear heterotopia to columnar heterotopia and are secondary to abnormalities of the neuroepithelium and failure to initiate migration. Although the exact pathophysiology remains to be elucidated, evidence suggests that injury to the neuroepithelium is an important factor in the formation of PVNH. Classic PVNH is associated with mutations in *FLNA*¹³. More recently, the phenotype of patients with *FLNA* related PVNH has been expanded to include a wide spectrum of connective tissue and vascular anomalies, including aortic root dilatation^{45,46}. Autosomal recessive forms of PVNH have been described in patients with mutations in *ARFGEF2*²⁹ and *C12orf57*^{47,48}. Other potential genetic loci for genes associated with PVNH include 7q11.23, 5p15.1, 5p15.33, 5q14.3-q15 and 4p15⁴⁹.

Lissencephaly And Subcortical Band Heterotopia—Abnormal transmantle migration can lead to agyria (complete absence of gyri), pachygyria (reduced but thickened gyri) (Figure 1B) and subcortical band heterotopia or double cortex syndrome (Figure 1C). Majority of lissencephaly cases are attributable to mutations in *LIS1* (also known as *PAFAH1B1*) and *DCX* and are commonly loss of function alleles. *LIS1* alleles include genic deletions, missense mutations and nonsense mutations, while *DCX* alleles include nonsense mutations, frameshifts, genic deletions, splicing mutation which are distributed across the entire length of the protein, whereas missense mutations cluster predominantly around the two functional microtubule binding domain and disrupt tubulin binding⁵⁰⁻⁵³. Germline null mutations in *LIS1* cause classic lissencephaly, while germline mutations in *DCX*, which is on the X-chromosome, results in lissencephaly in males and subcortical band heterotopia in females. Somatic mutations in *DCX* and *LIS1*, affecting as few as 10% of leukocytes, have been associated with variable degree of subcortical band heterotopia¹⁷.

With use of NGS, mutations in additional genes have been identified. These include *TUBA1A* (encoding a neuronal alpha tubulin)⁵⁴, *DYNC1H1* (encoding a dynein heavy chain isoform), *KIF2A* (encoding a kinesin heavy chain), *KIF5C* (encoding a member of the kinesin superfamily of proteins) and *TUBG1* (encoding gamma tubulin) and have been reported in patients with milder disease on the lissencephaly spectrum^{17,55}. These discoveries highlight the role of cytoskeletal proteins in neuronal migration. In addition, the complex of cytoplasmic dynein with Lis1, Nde1 and Ndel1 has been known to be essential for neuronal migration and more recently, patients with mutations in *NDE1* have been

reported in association with microlissencephaly, highlighting the link between microcephaly and lissencephaly²².

Cobblestone Malformations—Cobblestone malformations are associated with abnormal migration of neurons into the leptomeninges and are a result of deficiencies in the cerebral basement membrane due to defects in O-mannosylation of α -dystroglycan⁵⁶. This leads to abnormal cortical lamination and overmigration of neurons through the incomplete basement membrane into the pial layer². Mutations in multiple genes in the glycosylation pathway have been identified and mutations in the same gene can cause widely different phenotype⁵⁷. For example, mutations in *FKRP*, encoding a Fukutin-related protein, were initially identified in patients with only severe congenital skeletal muscle defects⁵⁸, but since have been identified in patients with milder skeletal system defects⁵⁹ and in patients with CNS malformations and eye involvement⁶⁰. More recently, genes associated with glycosylation within the endoplasmic reticulum (*SRD5A3*)⁶¹ or Golgi apparatus (*ATP6V0A2*)⁶², have also been reported in patients with cobblestone malformations.

Dystroglycanopathies can cause a wide range of disorders ranging from isolated brain malformation, to intellectual disability with microcephaly, and skeletal muscle and eye involvement. These syndromes are commonly referred to as Walker-Warburg syndrome, muscle-eye-brain disease, Fukuyama congenital muscular dystrophy and congenital muscular dystrophy type 1C and 1D depending on the extent of tissue involvement⁶⁰. However, elucidation of the genetic underpinnings has prompted a reclassification of the dystroglycanopathies⁵⁷.

Patients with mutations in *GPR56* can also cause cobblestone malformations but do not show a known glycosylation defect. *GPR56* is a G protein-coupled receptor that is preferentially expressed in the neuronal progenitor cells of the cerebral cortical ventricular and subventricular zones during periods of neurogenesis, but not in the cortical plate or intermediate zone. *GPR56* is postulated to regulate cortical patterning and patients with mutations in *GPR56* have thin cortex, suggesting a role in cell fate control during neurogenesis⁶³.

Polymicrogyria

Polymicrogyria (PMG) (Figure 1D) refers to a cerebral cortex with many excessively small gyri³. Etiology of PMG is highly heterogeneous and can be subdivided into: with schizencephalic clefts likely due to infection or vascular causes, without clefts but with and without associated CNS and non-CNS malformations and with certain types of inborn errors of metabolism (IEM)²

Polymicrogyria Without Clefts—PMG without clefts can be secondary to a genetic or disruptive process. Isolated PMG is classified by location; however, the genetic etiology remains unknown for majority of the PMG syndromes². The commonest form is bilateral perisylvian polymicrogyria, which presents with oromotor dysfunction, intellectual disability and epilepsy. The clinical presentation of patients with other forms of PMG vary widely and depend on the extent of PMG and presence of other brain malformations, such as cerebellar hypoplasia and/or microcephaly. PMG can affect cortical areas representing

language or primary motor functions, yet these functions can be retained with minimal or no disability³.

Copy number variants, especially deletion of chromosome 1p36.3 and chromosome 22q11.2, have been reported in association with PMG, although the causal genes remain to be identified. Common syndromic associations with PMG include Adams-Oliver syndrome⁶⁴, Joubert syndrome and related disorders⁶⁵, Goldberg-Shprintzen syndrome⁶⁶, Warburg Micro syndrome^{67,68} and Aicardi syndrome⁶⁹. Mutations in genes encoding α -tubulins, such as *TUBA8*⁷⁰, β -tubulins, such as *TUBB2B*⁷¹ and *TUBB3*⁷² have been reported in patients with PMG in isolation or in the presence of other brain malformations, including corpus callosum anomalies and optic nerve hypoplasia.

PMG like cortical malformations have also been reported in patients with inborn errors of metabolism, including peroxisomal disorders (such as Zellweger, neonatal adrenoleukodystrophy), fumaric aciduria, glutaric aciduria type 2, maple syrup urine disease and mitochondrial diseases^{2,3}. However, the pathomechanism of these associations is not well established. Some forms of PMG are also associated with the megalencephalic conditions and cobblestone disorders described above and so those genes should be considered in the differential genetic diagnosis.

Schizencephaly—In schizencephaly, the cortex edges can be fused (closed lip) or remain at a distance (open lip), and may be unilateral or bilateral. Patients with closed lip unilateral schizencephaly may present with hemiparesis or motor delay, while patients with open lip schizencephaly present with hydrocephalus or seizures³. Histologically, the cortex surrounding the cleft shows loss of laminar architecture, forming irregular heterotopic aggregates of grey matter. Although there was initial evidence of role of mutations in *EMX2* as a cause of schizencephaly⁷³, subsequent analysis has not further confirmed this^{74,75} and current understanding supports a non-genetic cause for most cases, likely infection (commonly, cytomegalovirus)⁷⁶ or vascular event⁷⁷. In addition, young maternal age and monozygotic twin pregnancies have been associated with higher incidence of schizencephaly⁷⁷.

DIAGNOSTIC STRATEGY

Brain imaging

In patients presenting with clinical features suggestive of MCD, diagnostic imaging with magnetic resonance imaging (MRI) is recommended to delineate the type of MCD³. The key features to look for include distribution and severity of MCD, the cortical surface and border between white and grey matter, cortical thickness and any other associated brain malformations (such as anomalies of corpus callosum, brainstem and cerebellum). Identification of the type of MCD will allow the clinician to focus on the malformation relevant genes.

Tissue consideration

Leukocyte derived DNA from peripheral blood is the most readily accessible tissue for genetic analysis in the clinic and will detect any inherited or *de novo* germline genomic

variants. However, in patients who present with a specific radiological phenotype but are negative on testing for the known malformation related genes, it is important to consider role of somatic mutations. In this scenario, DNA derived from buccal swabs has been shown to be more effective in detecting these mutations^{38,78}. However, some mutations require direct examination of the affected tissue (in this case, brain), which can be obtained from patients undergoing resection of the affected tissue, for example, for epilepsy surgery^{18,19}.

Genetic testing

Single nucleotide variants—In cases when 1 or 2 genes are known to be the predominant cause of MCD phenotype, for example, *LIS1* and *DCX* for lissencephaly and *FLNA* account for periventricular nodular heterotopia, targeted Sanger sequencing of these genes may still be the best approach, though targeted panels are increasingly the first line test. Given the known genetic heterogeneity of the MCD, such as in pachygyria or polymicrogyria, targeted gene panel are useful and cost effective, by efficiently analyzing multiple genes at once. An alternative strategy is to perform whole exome sequencing (WES), which is the process of sequencing the coding regions of the entire genome in one reaction and has been shown to improve diagnostic yield to 25% in undiagnosed cases with Mendelian disorder⁷⁹. However, one advantage of targeted gene panel sequencing is that the coverage of the genes of interest is more uniform than WES. Another advantage is that targeted gene panel obviates the issue related to incidental findings detected on WES (such as mutations in a *BRCA1* which may place the patient at risk for breast cancer in the future but are not related to primary phenotype)⁸⁰. Lastly, targeted gene panel sequencing also allows for deeper coverage, which in turn, is more likely to detect low frequency somatic mutations¹⁷.

Copy Number Variants—Copy number variants (CNVs) have been associated with certain forms of MCDs, including polymicrogyria. Traditionally, these CNVs were detected by cytogenetic analysis with karyotype and fluorescence in situ hybridization (FISH) analysis for specific regions of the genome. However, karyotype has a resolution of ~5 megabasepairs, and CNVs smaller than this are not detectable on karyotype. FISH is only specific for certain regions (for example, 22q11.2), but may be costly and laborious when probing multiple regions across the genome. The advantage of karyotype and FISH is that it provides structural information and can detect translocation. Translocations that disrupt genes of interest have been paramount in mapping of disease related genes over the past two decades.

More recently, chromosome microarray analysis (CMA) allows a clinician to detect submicroscopic CNVs across the entire genome. The diagnostic yield of CMA in patients with neurological disorders is ~10-15% and has replaced karyotype as the first tier test in evaluation of a child with multiple congenital anomalies, developmental delay and/or autism spectrum disorders⁸¹. Certain forms of CMA utilizing single nucleotide polymorphisms (SNPs) allow for detection of homozygosity in individuals with shared ancestry or consanguinity and can aid in narrowing the list of candidate genes⁸².

CURRENT MANAGEMENT OF THE DISEASE

Investigations

Brain imaging with MRI is the first step in managing any patient who presents with signs and symptoms of MCD. If the patient presents with seizures, electroencephalography (EEG) is prudent to detect any epileptogenic focus, which may be amenable to surgical resection. Other imaging modalities include diffusor tensor imaging (DTI) which can be used to better characterize the perturbation in brain development by evaluating the neuronal tracts⁸³ and functional MRI, including magnetoencephalography (MEG), which can be used to map brain activity and localize regions affected by pathology⁸⁴.

Management

The treatment of these individuals is predominantly symptomatic. Developmental delay is managed with neurorehabilitation, including physical and occupational therapy, and speech and feeding therapy. Learning disability should be managed based on the severity of learning disability and neurocognitive delay. This could range from additional help in regular school to special education classrooms. Patients with seizures need to be managed with appropriate anti-epileptic medications, under the guidance of a neurologist. Occasionally, patients with focal epileptogenic focus may benefit from surgical resection⁸⁵.

Genetic counselling should be provided to individuals and their families in whom a genetic cause is identified, and even in those who do not have an identifiable cause but the lesion is known to be genetic, either through a referral to a clinical geneticist or genetic counselor. In X-linked disorders, such as *DCX*, *FLNA* and *ARX*, the carrier mother may be completely asymptomatic and has a 50% risk of having another affected child. Similarly, disorders inherited with autosomal recessive inheritance, the couple has a 25% risk of having another affected child and 50% risk of having an unaffected but carrier child. For disorders with dominant inheritance, both parents should be assessed carefully with detailed physical examination and pertinent investigations, as some of these diseases can have variable expression even within a family. If the parents are affected, albeit mildly, they have 50% risk of having another affected child. However, if the parents are unaffected, the risk of them being mosaic carriers for the apparent *de novo* mutations is ~4%⁸⁶. In families with known molecular etiology, prenatal testing in the form of chorionic villus sampling or amniocentesis can be offered to guide subsequent pregnancies. Preimplantation genetic diagnosis (PGD) may also be an option for families in which the pathogenic variant has been identified.

FUTURE TREATMENT APPROACHES

Our understanding of the genes and pathways associated with MCDs is expanding rapidly. For example, recent identification of somatic mutations in the *PI3K-AKT-mTOR* pathway in patients with overgrowth related disorders offers potential opportunity for pharmacological intervention for these disorders, although this remains untested⁴¹. *mTOR* encodes the mammalian target for rapamycin and is used commonly as an immunosuppressant. The anti-epileptic effects of rapamycin have been evaluated in animal models of cortical dysplasia. For example, in mice with inactivated *TSC1*, rapamycin prevents epilepsy when given early

and ameliorates seizure activity when given at a later stage⁸⁷. In patients, administration of rapamycin has been demonstrated to show reduction in the duration and frequency of seizures in a child with tuberous sclerosis complex (TSC)⁸⁸, and has been associated with reduction in the size of the subependymal giant-cell astrocytomas in patients with TSC⁸⁹.

Similarly, patch clamp recordings from dysplastic neurons from patients with FCD type IIb show excitatory responses of GABA(A) receptors that are significantly attenuated by the SLC12A2 inhibitor bumetanide⁹⁰. This may be justify trials with bumetanide in patients with FCD on anticonvulsants that increase GABAergic function³.

With advances in genomic technology, our understanding of the molecular basis of these MCDs, including the diversity within each MCD and their associated secondary phenotypes, will continue to improve, which will allow for more rational and targeted treatment options. Identification of pathogenic variant can also allow for prenatal testing to guide future pregnancies in these families.

Acknowledgments

C.A.W. is supported by grants from the National Institute of Mental Health (R01MH083565 and 1RC2MH089952), the National Institute of Neurological Disorders and Stroke (R01NS032457, R01NS079277 and R01NS035129), the Simons Foundation, the Paul G. Allen Family Foundation, and the Manton Center for Orphan Disease Research. C.A.W. is an Investigator of the Howard Hughes Medical Institute.

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Key points

1. Development of cerebral cortex is a tightly regulated process and disruption in any part of this process can lead to malformations of cortical development (MCD).
2. MCD can primarily be classified into abnormalities of neurogenesis, abnormalities of neuronal migration and abnormalities of postmigrational development.
3. Recent advances in genomic technology have allowed for an unprecedented expansion in our knowledge of these disorders and have elucidated molecular pathways that can serve as targets for therapeutic interventions.

Figure 1. Axial MR images of the brain showing (A) periventricular nodular heterotopia (black arrows), (B) pachygyria (black arrows), (C) subcortical band heterotopia (arrowhead) and (D) polymicrogyria (white arrows).