Malformations of Cortical Development in Newborns: Genetic Aspects

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Contents

Abstract

The malformations of cortical development (MCD) represent a major cause of developmental disabilities, severe epilepsy, and reproductive disadvantage. Genes that have been associated to MCD are mainly involved in cell proliferation and specification, neuronal migration, and late cortical organization. Lissencephaly-pachygyria-severe band heterotopia are diffuse neuronal migration disorders (NMDs) causing severe, global neurological impairment. Abnormalities of the *LIS1*, *DCX*, *ARX,* and *RELN* genes have been associated with these malformations. Recent work has also established a relationship of lissencephaly, with or without associated microcephaly, corpus callosum dysgenesis, and cerebellar hypoplasia and, at times, a morphological pattern consistent with polymicrogyria with mutations of several genes (*KIF2A, KIF5C, TUBA1A, TUBA8, TUBB, TUBB2B, TUBB3, TUBG1,* and *DYNC1H1)* regulating the synthesis and function of microtubule and centrosome key components and hence defined as tubilinopathies. MCDs only affecting subsets of neurons, such as mild subcortical band heterotopia and periventricular heterotopia, cause neurological and cognitive impairment that vary from severe to mild deficits. They have been associated with abnormalities of the *DCX*, *FLN1A*, and *ARFGEF2* genes. Polymicrogyria results from abnormal late cortical organization and is inconstantly associated

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with abnormal neuronal migration. Localized polymicrogyria has been associated with anatomo-specific deficits, including disorders of language and higher cognition. Polymicrogyria is genetically heterogeneous and only in a small minority of patients has a definite genetic cause been identified. Megalencephaly with normal cortex by imaging, megalencephaly with polymicrogyria, dysplastic megalencephaly (including hemimegalencephaly), and focal cortical dysplasia can all result from mutations of the same genes in the PI3K-AKT-mTOR pathway which are often postzygotic and can be limited to the dysplastic tissue in the less diffuse forms.

List of Abbreviations

a > p	Anterior > posterior
BFPP	Bilateral frontoparietal PMG
BPP	Bilateral perisylvian PMG
CNV	Copy number variants
EEG	Electroencephalogram
ILS	Isolated LIS
LIS	Lissencephaly
MCD	Malformations of cortical development
MDS	Miller-Dieker syndrome
MLPA	Multiplex ligation-dependent probe amplification
MRI	Magnetic resonance imaging
p > a	Posterior > anterior
PMG	Polymicrogyria

Salient Points

- Malformations of cortical development (MCD) represent a major cause of developmental disabilities, severe epilepsy, and reproductive disadvantage.
- Genes associated with MCD are mainly involved in cell proliferation and specification, neuronal migration, and late cortical organization.
- Lissencephaly is characterized by absent (agyria) or decreased (pachygyria) convolutions, cortical thickening, and a smooth cerebral surface. Classical lissencephaly is rare, with a prevalence of about 12 per million births. Patients with severe lissencephaly have early developmental delay, hypotonia and later spastic quadriplegia, and eventual severe or profound mental retardation. Seizures occur in over 90% of children with lissencephaly, with onset before 6 months in about 75% of cases. Between 35% and 85% of children with classic lissencephaly develop infantile spasms, often without hypsarrhythmia.
- Lissencephaly-pachygyria-severe band heterotopia are diffuse neuronal migration disorders causing severe, global neurological impairment. Lissencephaly, subcortical band heterotopia, and lissencephaly with cerebellar hypoplasia are always genetic. Abnormalities of the *LIS1*, *DCX*, *ARX*, and *RELN* genes have been associated with these malformations.
- Mutations of several genes (KIF2A, *KIF5C*, *TUBA1A*, *TUBA8*, *TUBB*, *TUBB2B*, *TUBB3*, *TUBG1*, and *DYNC1H1*) that regulate the synthesis and function of microtubule and centrosome key components (and therefore called tubilinopathies) have been associated with lissencephaly, with or without associated microcephaly, corpus callosum dysgenesis, cerebellar hypoplasia, and polymicrogyria.
- MCDs only affecting subsets of neurons, such as mild subcortical band heterotopia and periventricular heterotopia, cause neurological and cognitive impairment that vary from severe to mild deficits. They have been associated with abnormalities of the *DCX*, *FLN1A*, and *ARFGEF2* genes.
- Polymicrogyria results from abnormal late cortical organization and is inconstantly associated with abnormal neuronal migration. Localized polymicrogyria has been associated with disorders of language and higher cognition. Polymicrogyria is genetically heterogeneous and only in a small minority of patients has a definite genetic cause been identified.
- Megalencephaly with a normal cortex on imaging, megalencephaly with polymicrogyria, dysplastic megalencephaly (including hemimegalencephaly), and focal cortical dysplasia can all result from mutations of the same

genes in the PI3K-AKT-mTOR pathway which are often postzygotic and, in the less diffuse forms, are limited to the dysplastic tissue.

Introduction

The development of the human cerebral cortex is a complex dynamic process that occurs during several gestational weeks (Gleeson and Walsh 2000). During the first stage, stem cells proliferate and differentiate into young neurons or glial cells deep in the forebrain, in the ventricular and subventricular zones lining the cerebral cavity. During the second stage, cortical neurons migrate away from their place of origin: most cells migrate along the radial glial fibers from the periventricular region towards the pial surface, where each successive generation passes one another and settles in an inside-out pattern within the cortical plate. When neurons reach their destination, they stop migrating and order themselves into specific "architectonic" patterns guiding cells to the correct location in the cerebral cortex. This third phase involves final organization within the typical six layers of cortex, associated with synaptogenesis and apoptosis.

Abnormal cortical development is increasingly recognized as a cause of developmental disabilities and epilepsy. This recognition is due, in part, to the improved use of magnetic resonance imaging (MRI), which makes it possible to assess the distribution and depth of cortical sulci, cortical thickness, the boundaries between gray and white matter, and variations in signal intensity. Abnormalities of any or all of these features may be observed in different malformations of cortical development (MCD), which may be restricted to discrete cortical areas or may, alternatively, be diffuse (Guerrini et al. 2008; Guerrini and Dobyns 2014).

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, and many inborn errors of metabolism. Importantly, a subset of MCD genes – especially those associated with megalencephaly – are associated with postzygotic (i.e., mosaic) mutations (Lee et al. 2012).

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.

In the following sections we will discuss the most frequent MCD.

Lissencephaly and Subcortical Band Heterotopia

Lissencephaly (LIS) is characterized by absent (agyria) or decreased (pachygyria) convolutions, cortical thickening, and a smooth cerebral surface (Guerrini and Dobyns 2014; Barkovich et al. 2012). Several types of LIS have been recognized. The most common, classical LIS, features a very thick cortex (10–20 mm vs. the normal 4 mm) and no other major brain malformations.

Subcortical band heterotopia (SBH) is a related disorder in which bands of gray matter are interposed in the white matter between the cortex and the lateral ventricles (Guerrini and Parrini 2010). Histopathology demonstrates that heterotopic neurons settle close to the "true" cortex in a pattern suggestive of laminar organization.

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.

Genetic Basis and Diagnosis

Lissencephaly, subcortical band heterotopia, and lissencephaly with cerebellar hypoplasia are always genetic. Studies to date have identified 12 lissencephaly genes (Table 1), which account for roughly 90% of patients. However, two major genes have been associated with classical LIS and SBH. The *LIS1* gene is responsible for the autosomal form of LIS (Cardoso et al. 2002), while the *DCX* gene is X-linked (Matsumoto et al. 2001). Although either gene can result in either LIS or SBH, most cases of classical LIS are due to deletions or mutations of *LIS1* (Cardoso et al. 2002), whereas most cases of SBH are due to mutations of *DCX* (Matsumoto et al. 2001). *LIS1*-related LIS is more severe in the posterior brain regions (p > a gradient) (Fig. 1a), whereas *DCX*-related LIS is more severe in the anterior brain (a > p gradient) (Fig. 1b).

About 60% of patients with p > a isolated LIS (ILS) carry genomic alterations or mutations involving *LIS1* (Mei et al. 2008). A simplified gyral pattern in the posterior brain, with underlying SBH, has been associated with mosaic mutations of *LIS1* (Cardoso et al. 2002). Miller-Dieker syndrome (MDS) is caused by deletion of *LIS1* and contiguous genes and features severe p > a LIS, accompanied by distinct dysmorphic facial features and additional malformations (Fig. 1c) (Cardoso et al. 2002).

Most *DCX* mutations cause a > p SBH/pachygyria. Mutations of *DCX* have been found in all reported pedigrees and in 80% of sporadic females and 25% of sporadic males with SBH (Matsumoto et al. 2001). Genomic deletions of *DCX* are rarely observed (Guerrini and Parrini 2010). Maternal germline or mosaic *DCX* mutations may occur in about 10% of cases of either SBH or XLIS (Gleeson et al. 2000). Hemizygous males with *DCX* mutations have classical LIS (Fig.1d), but rare boys with missense mutations and SBH have been described (Guerrini et al. 2003).

Phenotype

Classical LIS is rare, with a prevalence of about 12 per million births. Patients with severe LIS have early developmental delay, early diffuse hypotonia, later spastic quadriplegia, and eventual severe or profound mental retardation. Seizures occur in over 90% of LIS children, with onset before 6 months in about 75% of cases. Between 35% and 85% of children with classic lissencephaly develop infantile spasms, often without classic hypsarrhythmia. Most LIS children subsequently have multiple seizure types. In patients with MDS, classical LIS is accompanied by distinct dysmorphic facial features (Cardoso et al. 2002). The main clinical manifestations of SBH are mental retardation and epilepsy. Epilepsy is present in almost all patients and is intractable in about 65% of cases. About 50% of these epilepsy patients have focal seizures, and the remaining 50% have generalized epilepsy, often within the spectrum of Lennox-Gastaut syndrome (Guerrini and Parrini 2010).

Children with some lissencephaly syndromes (especially Miller-Dieker syndrome, and severe forms of lissencephaly with cerebellar hypoplasia or the X-linked syndrome of lissencephaly with abnormal genitalia) 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 lissencephaly with cerebellar hypoplasia, because all of these disorders are associated with better motor and cognitive function and longer survival (Dobyns et al. 2012).

Laboratory Investigations

In patients with classical LIS, the cytogenetic and molecular investigations are part of the diagnostic process. When MDS is suspected, a standard karyotype and FISH for the 17pl3.3 region is indicated. When isolated LIS is diagnosed, careful assessment of the antero-posterior gradient of

Table 1 Genes and chromosomal loci associated with MCD

Cortical malformation	Pattern of inheritance	Gene	Locus	OMIM
Lissencephaly (LIS)				
MDS	AD	*LIS1*	17p13.3	*601545
ILS or SBH	AD	*LIS1*	17p13.3	*601545
ILS or SBH	X-linked	*DCX*	Xq22.3-q23	*300121
ILS or SBH	AD	*TUBA1A*	12q12-q14	*602529
XLAG	X-linked	*ARX*	Xp22.13	*300382
LIS cerebellar hypoplasia	AR	*RELN*	7q22	*600514
LIS cerebellar hypoplasia	AR	*VLDR*	9p24.2	*192977
ILS	AD	*DYNC1H1*	14q32.31	*600112
ILS	AD	*KIF2A*	5q12.1	*602591
ILS	AD	*TUBA1A*	17q13.12	*602529
ILS	AD	*TUBB2B*	6p25.2	*612850
ILS	AD	*TUBG1*	17q21.2	*191135
Periventricular nodular heterotopia (PNH)				
Classical bilateral PNH	X-linked	*FLNA*	Xq28	*300017
Ehlers-Danlos syndrome and PNH	X-linked	*FLNA*	Xq28	*300017
Facial dysmorphisms, severe constipation, and PNH	X-linked	*FLNA*	Xq28	*300017
Fragile-X syndrome and PNH	X-linked	*FMR1*	Xq27.3	*309550
Microcephaly and PNH	AR	*ARFGEF2*	20q13.13	*605371
Donnai-Barrow syndrome and PNH	AR	*LRP2*	2q24-q31	*600073
PNH with limb abnormalities (limb reduction abnormality or syndactyly)	X-linked	. . .	Xq28	
Williams syndrome and PH	AD	. . .	7q11.23	
PH	AD	. . .	5p15.1	
PH	AD	. . .	5p15.33	
Agenesis of the corpus callosum, polymicrogyria, and PNH	AD	. . .	6q27 (C6orf70)	
PH	AD	. . .	6p25	
PH	AD	. . .	4p15	
PH	AD	. . .	5q14.3-q15	
PH	AD	. . .	22q11	
PH and steroid sulfatase deficiency	AD	. . .	Xp22.3	
PH	AD	. . .	Xp22.11	
PH and Smith-Magenis syndrome	AD	. . .	17p11.2	
Agenesis of the corpus callosum and PNH	AD	. . .	1p36.22-pter	
Polymicrogyria (PMG)				
Bilateral frontoparietal PMG	AR	*GPR56*	16q13	*604110
Asymmetric PMG	AD	*TUBB2B*	6p25.2	*612850
PMG and rolandic seizures, oromotor dyspraxia	X-linked	*SRPX2*	Xq21.33-q23	*300642
PMG and agenesis of the corpus callosum (ACC), microcephaly	AD	*TBR2*	3p21.3-p21.2	*604615
PMG and aniridia	AD	*PAX6*	11p13	*607108
PMG and microcephaly	AR	*NDE1*	16p13.11	*609449
PMG and microcephaly	AR	*WDR62*	19q13.12	*613583

(*continued*)

Table 1 (continued)

Cortical malformation	Pattern of inheritance	Gene	Locus	OMIM
PMG and fumaric aciduria	AR	*FH*	1q43	*136850
PMG and "band-like calcifications"	AR	*OCLN*	5q13.2	*602876
Perysilvian PMG and CHARGE syndrome	AD	*CHD7*	8q12.1-q12.2	*608892
PMG and Warburg micro syndrome	AR	*RAB3GAP1*	2q21.3	*602536
PMG and Warburg micro syndrome	AR	*RAB3GAP2*	1q41	*609275
PMG and Warburg micro syndrome	AR	*RAB18*	10p12.1	*602207
PMG-like, microcephaly, ACC	AD	*DYNC1H1*	14q32.31	*600112
PMG-like, microcephaly, ACC	AD	*KIF5C*	2q23.1	*604593
PMG-like, microcephaly, ACC, CBLH	AD	*TUBA1A*	17q13.12	*602529
PMG-like, microcephaly, ACC, CBLH	AR	*TUBA8*	22q11.21	*605742
PMG-like, microcephaly, ACC, CBLH	AD	*TUBB3*	16q24.3	*602661
PMG-like, microcephaly, ACC, CBLH	AD	*TUBB*	6p21.33	*191130
PMG-like, microcephaly, ACC	AR	*EOMES*	3p24.1	*604615
PMG and Goldberg-Shprintzen syndrome	AR	*KIAA1279*	10q21.3	*609367
PMG	AD	. . .	1p36.3-pter	
PMG and microcephaly	AD	. . .	1q44-qter	
PMG and facial dysmorphisms	AD	. . .	2p16.1-p23	
PMG and microcephaly, hydrocephalus	AD	. . .	4q21-q22	
PMG	AD	. . .	21q2	
PMG	AD	. . .	6q26-27	
PMG	AD	. . .	13q3	
PMG	AD	. . .	18p11	
PMG and Di George syndrome	AD	. . .	22q11.2	
Bilateral perysilvian PMG	AD	*PIK3R2*	19p13.11	*603157
Megalencephaly-polymicrogyria and dysplastic megalencephaly				
MPPH, DMEG	AD	*AKT3*	1q43q44	*611223
Weaver syndrome	AD	*EZH2*	7q36.1	*601573
MCAP	AD	*PIK3CA*	3q26.32	*171834
MPPH	AD	*PIK3R2*	19p13.11	*603157

AD autosomal dominant, *AR* autosomal recessive, *ACC* agenesis of the corpus callosum, *CBLH* diffuse cerebellar hypoplasia, *MPPH* megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome, *DMEG* dysplastic megalencephaly, *MCAP* megalencephaly-capillary malformation syndrome
*=gene/locus MIM number

cortical pattern abnormality will be suggestive of the involvement of either the *LIS1* or the *DCX* gene. When LIS is more severe posteriorly, it is worth performing first MLPA in order to rule out *LIS1* deletions/duplications. If a deletion/duplication is not found, *LIS1* sequencing should then be performed. In boys whose MRI shows more severe pachygyria in the frontal lobes, sequencing of the *DCX* gene is indicated. In patients with SBH direct sequencing of *DCX* should be performed. If a *DCX* mutation is not found, MLPA analysis should then be performed. Direct sequencing is also indicated in the mothers of patients harbouring a *DCX* mutation or other female relatives.

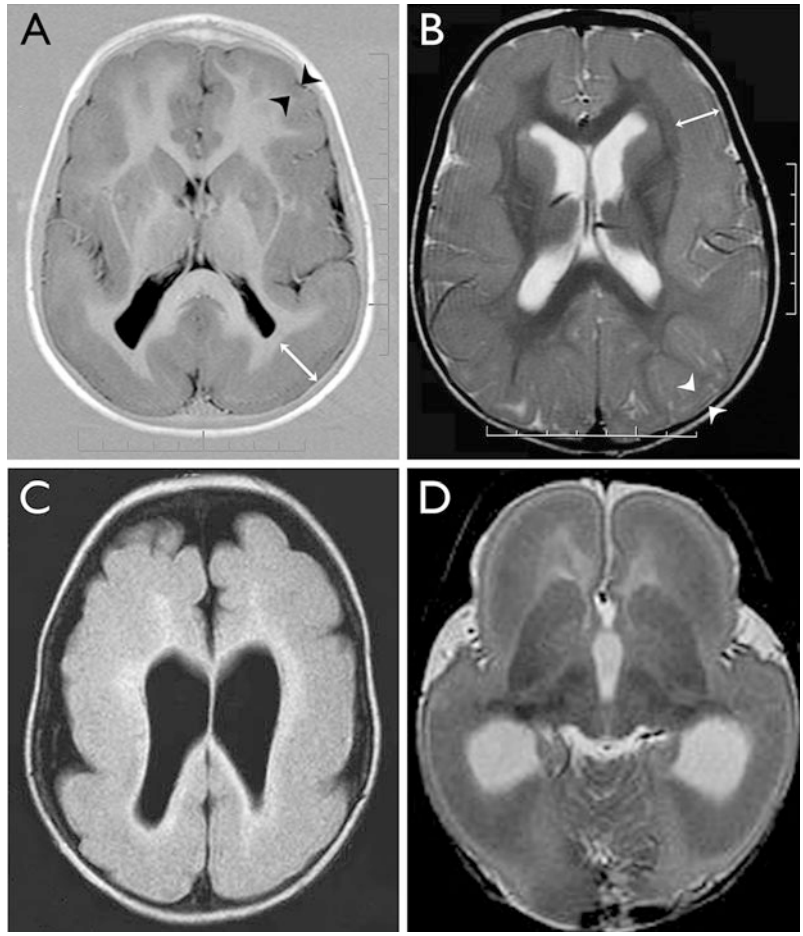

Fig. 1 Brain MRI of four different patients; axial sections: (**a**) classical LIS in a boy with *LIS1* gene mutation; (**b**) LIS in a girl with *DCX* mutation. In (**a**), there is a p > a gradient, cortical thickness is around 6 mm in the frontal lobes (*two black arrowheads*) and around 3 cm in the posterior brain (*white arrow*). In (**b**), there is a typical ar > p pattern; cortical thickness is around 2 cm in the frontal lobes (*white arrow*) and around 4 mm in the posterior brain (*two white arrowheads*). (**c**) LIS in a patient with MDS. (**d**) Severe diffuse LIS with relatively small frontal lobes in a boy with *DCX* mutation

Genetic Counseling

All reported *LIS1* alterations are *de novo*. Given the theoretical risk of germline mosaicism in either parent (which has never been demonstrated for *LIS1*), a couple with a child with lissencephaly is usually given a 1% recurrence risk.

When a *DCX* mutation is found in a boy with LIS, mutation analysis of *DCX* should be extended to the proband's mother, even if her brain MRI is normal. If the mother is a mutation carrier, the mutation will be transmitted according to Mendelian inheritance. If the mother is not a carrier, she can still be at risk of germline mosaicism; the risk of transmitting the mutation might roughly be estimated at around 5%.

Heterotopia

There are three main groups of heterotopia: periventricular (usually nodular: PNH), subcortical, and leptomeningeal, of which only the first two can be detected by imaging. PNH is by far the most frequent. SBH is a mild form of LIS and classified in that group.

Periventricular Nodular Heterotopia (PNH)

PNH consists of nodules of gray matter located along the lateral ventricles with a total failure of migration of some neurons (Guerrini and Dobyns 2014; Barkovich et al. 2012); it ranges from

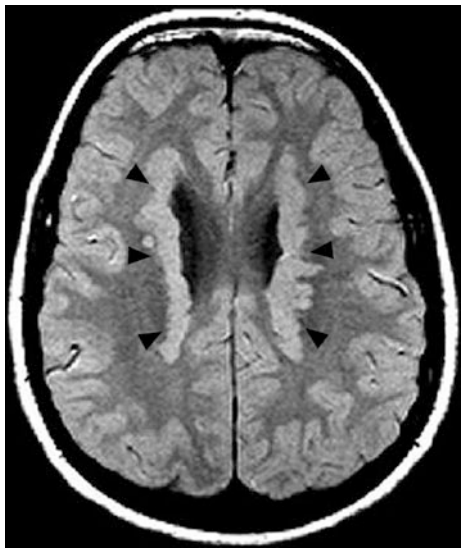

Fig. 2 Brain MRI: Axial section. Typical, classical bilateral PNH in a woman with a missense FLNA mutation. Bilateral nodules of subependymal heterotopia are contiguous and rather symmetric, extensively lining the ventricular walls (*black arrows*)

isolated, single, to confluent bilateral nodules (Fig. 2). The overlying cortex may show an abnormal organization. When the nodules are bilateral and numerous, a genetic basis is probable and other brain malformations are often reported (Parrini et al. 2006).

Genetic Basis and Diagnosis

PNH is a clinically and genetically heterogeneous disorder occurring most frequently in women as an X-linked trait (classical bilateral PNH), associated with high rates of prenatal lethality in male fetuses and 50% recurrence risk in the female offspring. Almost 100% of families and 26% of sporadic patients harbor mutations of the *FLNA* gene (Parrini et al. 2006), which also causes cardiovascular abnormalities in some patients of both sexes and gut malformations in boys. Only a few living male patients with PNH owing to *FLNA* mutations have been reported (Guerrini et al. 2004).

A rare recessive form of PNH owing to mutations of the *ARFGEF2* gene was described in two consanguineous pedigrees (Sheen et al. 2004) in which affected children had microcephaly, severe delay, and early-onset seizures.

Other genetic forms of periventricular nodular heterotopia have been mapped to several chromosomal loci (Table 1), but a putative causal gene has only been identified for the 6q27-related form (Conti et al. 2013).

Phenotype

Although most patients with PNH come to medical attention because they have focal epilepsy of variable severity, there is a wide spectrum of clinical presentations, including several syndromes with mental retardation and dysmorphic facial features. There is some correlation between the size of PNH and the likelihood of concomitant structural abnormality of the cortex and clinical severity (Parrini et al. 2006) but there seem to be no correlation between the size and number of heterotopic nodules and cognitive outcome. Most female patients with PNH due to *FLNA* mutations have epileptic seizures, with normal or borderline cognitive level. However, patients with even small isolated nodules caused by unknown genetic abnormalities or by copy number variations and severe cognitive impairment have been reported.

Laboratory Investigations

FLNA mutation analysis should be performed in patients with "classical" bilateral PNH. When autosomal recessive PH associated with microcephaly is suspected, *ARFGEF2* mutation analysis should be performed. Patients with PH associated with other brain malformations or extraneurological defects should be studied with array-CGH as genomic deletions/duplications have often been associated to PH.

Genetic Counseling

Classical PNH is much more frequent in women and likely to be due to *FLNA* mutations. Among

carrier women, about half have *de novo FLNA* mutations, whereas the remaining half have inherited mutations. Although maternal transmission is much more likely, father-to-daughter transmission is possible. Given that germline mosaicism of *FLNA* has never been reported, the recurrence risk (for other children) seems to be very low when a mutation is found in the proband but neither parent is a carrier. Counseling is very difficult when PNH is not related to either *FLNA* or *ARFGEF2;* array-CGH study for the search of copy number variations is advised. The number of known cases of familial PNH unrelated to these genes is extremely low.

Polymicrogyria Phenotypes and Genetics

The term "polymicrogyria" (PMG) defines an excessive number of abnormally small gyri that produce an irregular cortical surface with lumpy aspect (Lee et al. 2012). Polymicrogyria can be localized to a single gyrus, involve a portion of one hemisphere, be bilateral and asymmetrical, bilateral and symmetrical or diffuse. The imaging appearance of polymicrogyria varies with the patient's age. In newborns and young infants, the malformed cortex is very thin with multiple, very small undulations. After myelination, polymicrogyria appears as thickened cortex with irregular cortex-white matter junction (Guerrini et al. 2008; Guerrini and Dobyns 2014).

The clinical manifestations of polymicrogyria vary widely and depend on several factors. The most severe outcomes occur in children with severe microcephaly (−3SD 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 localized 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 (Guerrini and Barba 2010).

Polymicrogyria is associated with a wide number of patterns and syndromes and with mutations in several genes (Table 1). Various PMG syndromes have been described, which have been designated according to their lobar topography (Barkovich et al. 2012).

Bilateral perisylvian polymicrogyria (BPP) (Fig. 3a, b) is the most frequent form. It is associated with mild to moderate mental retardation, epilepsy, and impaired oromotor skills. Most cases are sporadic but genetic heterogeneity is suggested (Barkovich et al. 2012). BPP, frequently asymmetric and with a striking predisposition for the right hemisphere, has also been reported in children with 22q11.2 deletion (Barkovich et al. 2012). Recently, mutations in *PIK3R2*, a regulatory subunit of the PI3K-AKT-mTOR pathway, have been associated with BPP (Mirzaa et al. 2015).

Bilateral frontoparietal polymicrogyria (BFPP) (Fig. 3c) has been reported in families with recessive pedigrees and has been associated with mutations of the *GPR56* gene (Piao et al. 2004). The imaging characteristics of BFPP resemble those of the cobblestone malformative spectrum (muscle-eye-brain disease and Fukuyama congenital muscular dystrophy) (Barkovich et al. 2012).

Some copy-number variants have been associated with polymicrogyria (Table 1), but only deletions in 1p36.3 and 22q11.2 are common (Dobyns et al. 2008; Robin et al. 2006). 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 (Robin et al. 2006).

Tubulinopathies and Related Disorders

Classic lissencephaly and polymicrogyria have long been thought of as distinct disorders, but they 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 (i.e., much earlier than the genes usually associated with polymicrogyria and schizencephaly) (Jaglin et al. 2009; Poirier et al.

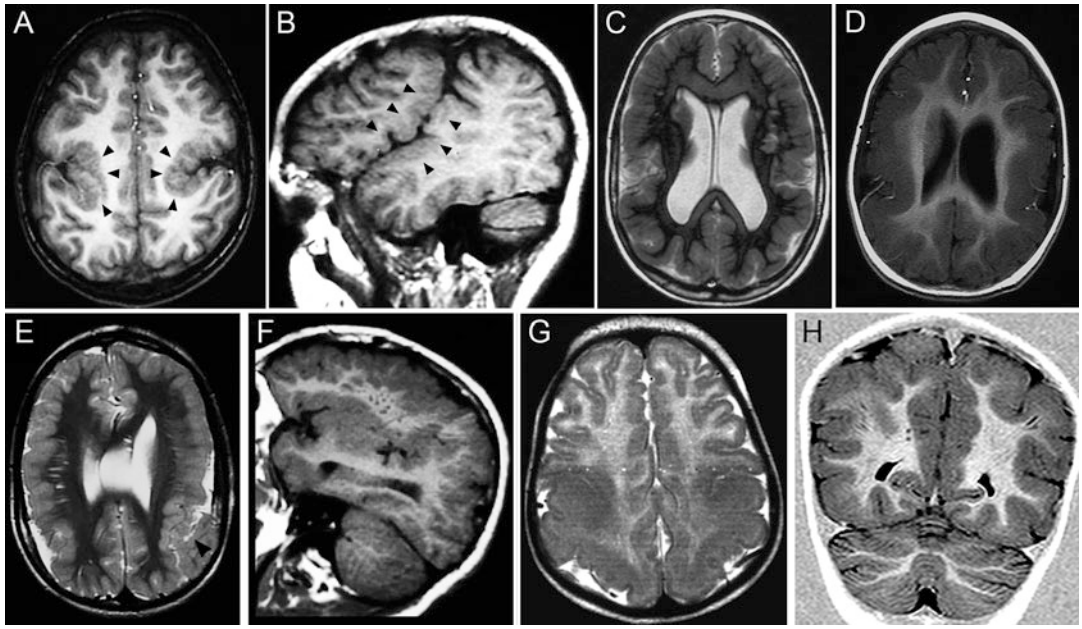

Fig. 3 Brain MRI scan in patients with PMG or tubulinophaties. (**a**) Axial section and (**b**) Sagittal section in a patient with BPP. The sylvian fissures are open and the perisylvian cortex is thickened and irregular (*black arrows*). Note the abnormally vertical orientation of the sylvian fissure, which appears to be fused with the rolandic fissure. (**c**) Axial section. BFPP in a girl with a *GPR56* mutation and Lennox-Gastaut syndrome. (**d**) Axial section in a patient with a symplified gyral pattern and *TUBA1A* mutation. (**e**) Axial and (**f**) sagittal section in a patient with cortical thickening, diffuse polymicrogyira, and *TUBB2B* mutation. (**g**) Axial section in a patient with posterior pachygyria and *DYNC1H1* mutation. (**h**) Coronal section in a patient with posterior pachygyria, cortical thickening, and *DYNC1H1* mutation

2013; Cushion et al. 2013). The full range of these malformations vary from extreme lissencephaly with completely absent gyri, total agenesis of the corpus callosum, and severe cerebellar hypoplasia, to less severe lissencephaly with moderate-to-severe cerebellar hypoplasia, to classic lissencephaly, to an atypical polymicrogyria-like cortical malformation with cerebellar hypoplasia (Fig. 3d–h). By definition, tubulinopathies are always genetic. Investigators have identified nine genes (*KIF2A, KIF5C, TUBA1A, TUBA8, TUBB, TUBB2B, TUBB3, TUBG1,* and *DYNC1H1*; Table 1), 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 traffcking activities of the microtubule-dependent molecular motors KIF2A, KIF5C, and DYNC1H1 in postmitotic neuronal cells (Poirier et al. 2013).

AICARDI SYNDROME is exclusively observed in females, with the exception of two reported males with two X-chromosomes and is thought to be caused by an X-linked gene with lethality in the hemizygous male. However, the genetic basis is still unknown. Clinical features include severe mental retardation, infantile spasms, and chorioretinal lacunae. Neuropathological findings are consistent with a neuronal migration disorder and include diffuse unlayered polymicrogyria with fused molecular layers, agenesis of the corpus callosum, and nodular heterotopias in the periventricular or subcortical region. Microgyri are packed and usually not visible at MRI (Fig. 4) (Sutton and Van den Veyver 2006). The

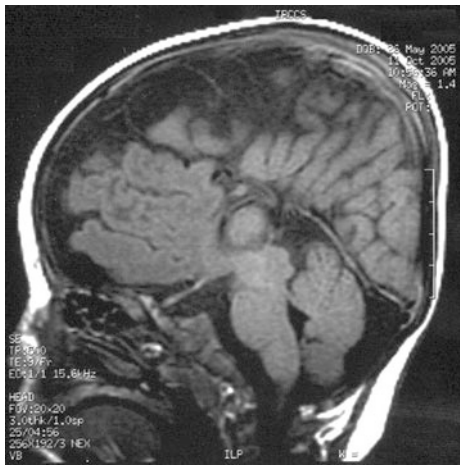

Fig. 4 T1 weighted sagittal MRI scan of the brain of a 5-months-old girl with Aicardi syndrome and intractable infantile spasms. Note the extremely hypoplastic corpus callosum with an extensive area of polymicrogyria involving the frontal lobe. There is a posterior fossa cyst

specific cause of Aicardi syndrome has not yet been identified.

Megalencephaly, Dysplastic Megalencephaly, and FCD Type 2

The term megalencephaly refers to an abnormally large brain that exceeds the mean for age and gender by 2 SD (DeMyer 1986). 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), and FCD can all result from mutations of the same genes in the PI3K-AKT-mTOR pathway (Lee et al. 2012; Poduri et al. 2012; Rivière et al. 2012). Dysplastic megalencephaly includes all forms of segmental brain overgrowth with cortical dysplasia. 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. 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 (Blümcke et al. 2011). 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 (Crino 2009). This hypothesis has been in part confirmed by recent studies documenting pathogenic germline and somatic mosaic mutations in the *MTOR* gene or in other genes belonging to the PI3K-AKT-mTOR pathway in the dysplasic tissue of FCD type 2a and 2b (D'Gama et al. 2015; Lim et al. 2015). In almost all patients with FCD type 2, the lesion is detected after onset of focal epilepsy. A growing number of syndromes and genes have been associated with megalencephaly, especially with more severe phenotypes (Mirzaa et al. 2012a). Megalencephaly without cortical malformations occurs in benign autosomal dominant macrocephaly, a poorly defined disorder. 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*) (Mirzaa et al. 2015; Mirzaa et al. 2012b). Dysplastic megalencephaly most often occurs without syndromic features and has recently been associated with mosaic mutations of *PIK3CA*, *AKT3*, and *MTOR* (Lee et al. 2012).

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