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Classification system for malformations of cortical development

Update 2001

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Article abstract—The many recent discoveries concerning the molecular biologic bases of malformations of cortical development and the discovery of new such malformations have rendered previous classifications out of date. A revised classification of malformations of cortical development is proposed, based on the stage of development (cell proliferation, neuronal migration, cortical organization) at which cortical development was first affected. The categories have been created based on known developmental steps, known pathologic features, known genetics (when possible), and, when necessary, neuroimaging features. In many cases, the precise developmental and genetic features are uncertain, so classification was made based on known relationships among the genetics, pathologic features, and neuroimaging features. A major change since the prior classification has been the elimination of the separation between diffuse and focal/multifocal malformations, based on the recognition that the processes involved in these processes are not fundamentally different; the difference may merely reflect mosaicism, X inactivation, the influence of modifying genes, or suboptimal imaging. Another change is the listing of fewer specific disorders to reduce the need for revisions; more detail is added in other smaller tables that list specific malformations and malformation syndromes. This classification is useful to the practicing physician in that its framework allows a better conceptual understanding of the disorders, while the component of neuroimaging characteristics allows it to be applied to all patients without necessitating brain biopsy, as in pathology-based classifications.

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Although cerebral cortical development is an extremely complex process, it can be divided into three broad and overlapping steps: cell proliferation, neuronal migration, and cortical organization. In 1996, a classification scheme for malformations of cortical development, based on the developmental step at which the developmental process was disturbed, was proposed.¹ At that time, the authors noted that the classification was not final, but that it provided a framework for classification of both known and undescribed malformations and that it would continue to be modified as our knowledge advanced. This classification has proved useful in helping those physicians who diagnose and treat patients with malformations of cortical development and has been adopted by many individuals in the field. Since then, substantial new information has accumulated concerning both normal and abnormal cortical development, particularly regarding the genetic basis and imaging features of many malformations of cortical development. For example, three lissencephaly genes²⁻⁵ and two cobblestone complex genes^{6,7} have

been mapped or cloned (table 1). The imaging features of all have been described^{2,8-12} or are known to the authors. One heterotopia gene has been identified (see table 1¹³) and the imaging features described.¹⁴ In addition, many other malformations and malformation syndromes have been recognized, based primarily on imaging criteria with some data on genetics and other clinical aspects. This recognition was made possible by both advances in imaging techniques that allow better morphologic analysis of dysplastic cortex¹⁵ and additional experience resulting from collaborative efforts among developmental neurogenetics, epileptology, and neuroimaging. For example, several distinct forms of primary microcephaly,^{16,17} lissencephaly,⁸ and polymicrogyria¹⁸⁻²¹ have been delineated, and still more have been recognized but not yet reported.

Recent observations have revealed a wide range of malformation phenotypes, from diffuse to multifocal to bilateral/symmetric to focal, among patients with the same underlying cause of malformation.²²⁻²⁷ It seems that a useful system of classification must

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Table 1 Genetic basis of malformations of cortical development

Syndrome	Locus	Gene	Protein	References
ILS ^{DCX}	Xq22.3-q23	<i>DCX = XLIS</i>	DCX or doublecortin	3, 4, 46
SBH ^{DCX}	Xq22.3-q23	<i>DCX = XLIS</i>	DCX or doublecortin	24, 26, 47
MDS	17p13.3	Several contiguous	PAFAH1B1 and others	112
ILS ^{LIS1}	17p13.3	<i>LIS1</i>	PAFAH1B1	5, 44, 46, 113
SBH ^{LIS1}	17p13.3	<i>LIS1</i>	PAFAH1B1	45
LCH ^{RELN}	7q22	<i>RELN</i>	reelin	2
FCMD ^{FCMD}	9q31	<i>FCMD</i>	FCMD or fukutin	6, 114
MEB	1p32	Unknown	Unknown	7, 28
BPNH	Xq28	<i>FLM1</i>	Filamin-1	13
TSC1	9q32	<i>TSC1</i>	hamartin	115, 116
TSC2	16p13.3	<i>TSC2</i>	tuberin	117, 118

ILS = isolated lissencephaly sequence; SBH = subcortical band heterotopia; MDS = Miller–Dieker syndrome; LCH = lissencephaly with cerebellar hypoplasia; FCMD = Fukuyama congenital muscular dystrophy; MEB = muscle–eye–brain disease; BPNH = bilateral periventricular nodular heterotopia.

place all malformations with the same known cause together. In addition, increasing experience has shown that malformations with nearly identical morphology and pathophysiology may have different genetic bases.^{28–33} A useful system must also segregate these genetically different malformations.

Finally, as our understanding of normal and abnormal cortical development progresses, the previous classification runs the risk of becoming inconsistent with current understanding of those developmental processes on which it is based. Under these circumstances, the classification can lose its value or become confusing if it is at odds with current literature. As a result of all of these factors, the authors undertook the task of updating the classification so that it might retain both its clinical and conceptual utility.

Updated classification. *Changes in framework.* The previous classification divided malformations of cortical development into three major groups: those resulting from abnormalities of cell proliferation, those resulting from abnormalities of neuronal migration, and those resulting from abnormal cortical organization.¹ These three fundamental groups have been retained with minor changes in our revised classification (table 2). It is important to remember that these three major steps are not temporally separate; proliferation continues after migration begins, and migration continues as organization commences. Nonetheless, these steps are useful in both conceptual and mechanistic understandings of the disorders.

Although the revised classification has retained these three fundamental groups, the terminology for Group 1 has been modified slightly. Group 1 is now referred to as Disorders of Cell Proliferation or Apoptosis. This change stems from our realization that apoptosis plays a critical role in the formation of the cerebral cortex.^{34–37} At our current stage of knowledge, it is not possible to differentiate abnormal

brain size secondary to abnormal proliferation from that secondary to abnormal apoptosis or, indeed, from a combination of both processes. Indeed, several recent papers have shown remarkable changes in brain development that result from perturbations of apoptosis.^{34,35}

The most significant change in this revised classification is in the subdivision of the three major categories. In the first classification, each of the three major categories was divided into (A) Diffuse Malformations and (B) Focal or Multifocal Malformations. This division has been eliminated in the revision. This change was based on several factors. First, we believe that the assessment of extent of disease is generally underestimated by imaging techniques. This is related both to the technique that is used and to the time taken to analyze the images.³⁸ Images acquired with thin contiguous sections, small interslice gaps, and increased signal-to-noise ratio will result in detection of subtle abnormalities that are otherwise missed.^{15,38–40} These missed lesions may partly explain why the authors found separation of diffuse from focal/multifocal anomalies to be unhelpful in the clinical environment.

More fundamentally, diffuse and localized brain malformations may result from the same underlying processes, specifically from mutations of the same causative genes. The differences in phenotype may be explained by 1) different mutations of the same gene that affect protein function differently, 2) different dosage of the same mutation in the same gene, and 3) different effects of the same mutation and dosage (variable expressivity) caused by unidentified modifying factors. Recent examples of each of these mechanisms have been reported.

First, mutation genes that abolish protein function, such as large deletions and truncations of the *LIS1* and *DCX*, usually cause more severe lissencephaly than missense mutations (base pair substitutions) that only reduce protein function, and

Table 2 Classification scheme

-
- I. Malformations due to abnormal neuronal and glial proliferation or apoptosis
 - A. Decreased Proliferation/Increased Apoptosis: Microcephalies
 - 1. Microcephaly with normal to thin cortex
 - 2. Microlissencephaly (extreme microcephaly with thick cortex)
 - 3. Microcephaly with polymicrogyria/cortical dysplasia
 - B. Increased Proliferation/Decreased Apoptosis (normal cell types): Megalencephalies
 - C. Abnormal Proliferation (abnormal cell types)
 - 1. Non-neoplastic
 - a. Cortical hamartomas of Tuberous sclerosis
 - b. Cortical dysplasia with balloon cells
 - c. Hemimegalencephaly (HMEG)
 - 2. Neoplastic (associated with disordered cortex)
 - a. DNET (dysembryoplastic neuroepithelial tumor)
 - b. Ganglioglioma
 - c. Gangliocytoma
 - II. Malformations due to abnormal neuronal migration
 - A. Lissencephaly/Subcortical Band Heterotopia Spectrum
 - B. Cobblestone complex
 - 1. Congenital muscular dystrophy syndromes
 - 2. Syndromes with no involvement of muscle
 - C. Heterotopia
 - 1. Subependymal (periventricular)
 - 2. Subcortical (other than Band Heterotopia)
 - 3. Marginal glioneuronal
 - III. Malformations due to abnormal cortical organization (including late neuronal migration)
 - A. Polymicrogyria and schizencephaly
 - 1. Bilateral polymicrogyria syndromes
 - 2. Schizencephaly (polymicrogyria with clefts)
 - 3. Polymicrogyria with other brain malformations or abnormalities
 - 4. Polymicrogyria or schizencephaly as part of Multiple Congenital Anomaly/Mental Retardation syndromes
 - B. Cortical dysplasia without balloon cells
 - C. Microdysgenesis
 - IV. Malformations of cortical development, not otherwise classified
 - A. Malformations secondary to inborn errors of metabolism
 - 1. Mitochondrial and pyruvate metabolic disorders
 - 2. Peroxisomal disorders
 - B. Other unclassified malformations
 - 1. Sublobar dysplasia
 - 2. Others
-

terior pachygyria only, or posterior-predominant subcortical band heterotopia. Patients with *DCX* mutations have an even wider range of phenotypes, from diffuse lissencephaly to partial subcortical band heterotopia.

Second, mosaic mutations are usually less severe than germ line mutations. In this context, mosaicism indicates that the mutation is present in some cells of the brain but not others (in contrast, germ line mutations are present in all cells of the organism). Depending on protein expression, this could mean that protein function is only partly reduced (i.e., from 100 to 80% rather than 100 to 50%) in regions where it is expressed or that protein function is greatly reduced but in only some cells in the region of expression. This mechanism applies to both somatic mosaicism, in which the mutation is present in some cells but not others, and to X inactivation, in which the mutation is present in all cells with two (or more) X chromosomes but is active in some cells and not in others. The latter results in functional mosaicism such that affected females with *DCX* mutations are always less severely affected than their affected male relatives. Both somatic and functional (X inactivation related) mosaicism appear to be causes of phenotypic heterogeneity among patients with malformations due to mutations of the *DCX* gene^{41,43,47,48} (also W.B. Dobyns, unpublished data).

Finally, large deletions of the DiGeorge critical region in chromosome 22q11.2 have been reported in at least six patients with polymicrogyria.^{22,23,49-51} Unexpectedly, the polymicrogyria has been asymmetric in four of six patients, including in three patients more severe on the right, one more severe on the left, and two symmetric, despite having the same molecular abnormality. At least two of their parents carried the same 22q11.2 deletion. Together, these observations support both incomplete penetrance and variable expressivity with the same molecular lesion. Such striking differences in phenotype despite the presence of the same mutation imply that other “modifying” factors must be at work.

Further, the recognition of such mechanisms is of great importance in genetic counseling. Patients with severe germ line mutations such as deletions and truncations typically have severe phenotypes that preclude reproduction, resulting in a low recurrence risk. Somatic mosaic mutations often have a mild phenotype but have a postzygotic origin and are thus not inherited from parents. This again results in a low recurrence risk. Thus, the highest recurrence risks are usually found in patients and families with germ line missense mutations. This is certainly true for patients with mutations of the *DCX* lissencephaly gene. This classification has the flexibility to allow these components of genetics to be integrated as they are discovered. For the present, we believe that the classification in its current form is optimal.

We have further changed our approach to the classification by listing fewer specific disorders in the

similarly nonconservative (i.e., acidic to basic) amino acid substitutions are more severe than conservative changes.^{24,26,41-46} Specifically, patients with different *LIS1* mutations may have diffuse lissencephaly, pos-

Table 3 Classification of the congenital microcephalies* and megalencephaly

-
- I. Malformations due to abnormal neuronal and glial proliferation or apoptosis
- A. Decreased proliferation
1. Microcephaly with normal to thin cortex
 - a. Primary microcephaly (microcephaly vera), NOC
 - b. Extreme microcephaly with simplified gyral pattern (MSG)
 2. MicroliSSencephaly (extreme microcephaly with thick cortex)
 - a. MLIS with thick cortex (Norman–Roberts syndrome)
 - b. MLIS with thick cortex, severe brainstem and cerebellar hypoplasia (Barth MLIS syndrome)
 - c. MLIS with intermediate cortex, abrupt AP gradient
 - d. MLIS with mildly to moderately thick (6–8 mm) cortex
 3. Microcephaly with polymicrogyria or other cortical dysplasias
 - a. Extreme microcephaly with diffuse or asymmetric polymicrogyria
 - b. Extreme microcephaly with ACC and cortical dysplasia
- B. Increased proliferation
1. Megalencephaly (anatomic)
 2. Megalencephaly-polymicrogyria-hydrocephalus syndrome
-

* Extreme microcephaly defined as -3 SD or smaller at birth.

ACC = agenesis of the corpus callosum.

main classification (see table 2). This should make future revisions less frequent. More detail is added in other smaller tables that list specific malformations and malformation syndromes. These small tables allow updating of the classification without unnecessarily modifying the framework of the classification system.

Revised classification. Group I: Malformations due to abnormal proliferation/apoptosis. The mechanisms by which these malformations occur are complex and poorly understood. Cell proliferation is the process that takes place in the germinal zones of the developing prosencephalon. Prior to neurogenesis, the pool of progenitor cells is expanded through a series of cell divisions in which both daughter cells re-enter the cell cycle as progenitors. Eventually, under the influence of signals that are not yet known, the fraction of postmitotic cells that exits the cell cycle to become neurons or glia gradually increases until the proliferative potential of the germinal zone is exhausted. Glial precursors that arise in the germinal zone may continue to proliferate in the overlying cerebral wall over much of the life of the organism. Certain proteins that have a role in this differentiation have been identified in *Drosophila*.⁵² The major organizational change in this group, other than the general changes already discussed, is a reorganization of patients with microcephaly (defined as head circumference 2 SD or more below the age-

Table 4 Malformations due to abnormal proliferation with abnormal cell types

-
- I. Malformations due to abnormal neuronal and glial proliferation or apoptosis
- C. Abnormal proliferation (abnormal cell types)
1. Non-neoplastic
 - a. Cortical hamartomas (tubers) of tuberous sclerosis
 - i. Chromosome 9-linked (TSC1 mutations)
 - ii. Chromosome 16-linked (TSC2 mutations)
 - b. Cortical dysplasia with balloon cells
 - c. Hemimegalencephaly (HMEG)
 - i. Isolated hemimegalencephaly
 - ii. HMEG in neurocutaneous disorders
 2. Neoplastic (associated with disordered cortex)
 - a. DNET (dysembryoplastic neuroepithelial tumor)
 - b. Ganglioglioma
 - c. Gangliocytoma
-

matched norm, Group I.A; see tables 2 and 3). In our previous classification, all children with generalized decreased proliferation were classified as having microliSSencephaly. Since then, a number of groups of patients with extreme congenital microcephaly, currently defined as occipitofrontal circumference of 3 or more SD below the mean at birth, have been identified.^{16,17} This extreme microcephaly, in the absence of evidence of in utero injury, is presumably secondary to decreased proliferation or increased apoptosis of cells. The best defined groups at present include Microcephaly with Simplified Gyral Pattern^{16,17} and MicroliSSencephaly,¹⁷ although other primary microcephalies that are not otherwise classified are also included. We place neonates with microcephaly between 2 and 3 SD below the mean in the Microcephaly Not Otherwise Classified group because the other groups were defined as being 3 or more SD below mean; we recognize, however, that this distinction is rather arbitrary and that some overlap is likely. Each of these groups is rather complex and contains what are likely to be many different genetic malformations (see table 3).

In our prior classification, we included no examples of disorders with increased proliferation of normal cell types. One possible malformation in this group has recently come to our attention. It consists of congenital megalencephaly, polymicrogyria, and hydrocephalus. Although no pathology data are currently available, the abnormal MRI signal typically seen in patients with disorders due to abnormal cell proliferation was not seen.

Note that all non-neoplastic malformations secondary to abnormal proliferation (Group I.C.1) (table 4) are characterized histologically by the presence of balloon cells, large cells containing large volumes of cytoplasm that may stain for neuronal markers, glial markers, both, or neither. The origin of balloon cells is uncertain. Most studies have interpreted them as cells that failed to differentiate at a very early (stem

cell) stage.⁵³ As a consequence, they seem to be excellent markers for malformations secondary to stem cell maldifferentiation. The cortical hamartomas of tuberous sclerosis are included in this category (I.C.1.a), despite the occurrence of giant cell tumors in 5 to 10% of affected individuals and the known occurrence of extra CNS neoplasia in this syndrome. We justify this classification on the grounds that the giant cell tumors develop from the subependymal nodules, which have a very heterogeneous population of cells and are not considered cortical malformations. Tumors are not known to develop from the cortical hamartomas, also called tubers, which have features very similar, if not identical, to those of cortical dysplasia.^{54–58} The classification clearly states that it applies only to the cortical hamartomas to obviate confusion on this point.

In the previous version of our classification, we listed hemimegalencephaly associated with epidermal nevus syndrome, hypomelanosis of Ito, and Klippel–Trenaunay syndrome as specific entities that were distinct from isolated hemimeganencephaly and from hemimeganencephaly associated with neurocutaneous syndromes. We have become aware, since then, that the boundaries of these conditions are not well defined. Indeed, epidermal nevus syndrome comprises several phenotypes associated or not with systemic anomalies, whereas hypomelanosis of Ito may merely represent a nonspecific manifestation (i.e., a phenotype) of chromosomal mosaicism. Moreover, there is current evidence that the Klippel–Trenaunay syndrome is part of a spectrum of vascular disorders that may be explained by mosaicism.^{59–61} In addition, several reports have demonstrated the association of hemimeganencephaly with proteus syndrome^{62,63} and focal alopecia⁶⁴ and the presence of hemimeganencephaly in some cases of neurofibromatosis type 1⁶⁵ and tuberous sclerosis.⁶⁶ As a result, we have chosen to modify the classification of hemimeganencephaly to include only two subtypes, Isolated Hemimeganencephaly (I.C.1.c.i) and Hemimeganencephaly Associated with Neurocutaneous Disorders (I.C.1.c.ii).

Group II: Malformations due to abnormal migration. Our knowledge of mechanisms by which malformations may occur has advanced more for this group than for any other. Neuronal migration requires the migrating neuron to attach to radial glial cells that span the developing hemisphere, migrate along the radial glial cells, and detach when they reach the proper layer of the developing cerebral cortex. Nonradial or tangential migration also occurs, but probably involves mainly GABAergic interneurons.^{67,68} Several proteins have been identified that play important roles in these steps. The Filamin-1 gene encodes an actin-cross-linking phosphoprotein, which transduces ligand–receptor interactions at the cell surface to actin reorganization in the cytoskeleton. Without actin cross-linking, the migrating neurons cannot extend their growth cones along radial glia cells and neuronal migration cannot begin.¹³ The

Table 5 Classification of the lissencephalies

-
- II. Malformations due to abnormal neuronal migration
- A. Lissencephalies/Subcortical Band Heterotopia Spectrum
1. Classical lissencephaly (agyria-pachygyria) and subcortical band heterotopia (SBH)
 - a. Miller–Dieker syndrome (MDS) with deletions of *LIS1* and telomeric genes
 - b. Lissencephaly or SBH with *LIS1* mutations
 - c. Lissencephaly or SBH with *DCX* (*XLIS*) mutations
 - d. Baraitser–Winter syndrome (BWS)
 - e. Other lissencephaly and SBH loci
 2. Lissencephaly with agenesis of the corpus callosum (LACC)
 - a. LACC with neonatal death
 - b. LACC
 - c. X-linked LACC with abnormal genitalia (XLAG)
 3. Lissencephaly with cerebellar hypoplasia (LCH)
 - a. LCH identical to classical LIS except moderate vermis hypoplasia
 - b. LCH with AP gradient, malformed hippocampus, and globular cerebellum
 - i. LCH with *RELN* mutations
 - ii. Other loci
 - c. LCH with severe brainstem and cerebellar hypoplasia, and neonatal death
 - d. LCH with brainstem and cerebellar hypoplasia
 - e. LCH with abrupt AP gradient
 - f. LCH with agenesis of the corpus callosum, brainstem and cerebellar hypoplasia
 4. Lissencephaly, NOC
 - a. Lissencephaly with T cell deficiency
 - b. Winter–Tsukahara syndrome (WTS)
-

DCX (or *XLIS*) and *LIS1* genes produce proteins known as doublecortin and PAFAH1B1 (platelet-activating factor acetylhydrolase β subunit). Both are postulated to regulate microtubule organization and function, which appears to be critical for neuronal migration to occur. Different mutations of these genes may result in agyria, pachygyria, or band heterotopia.^{45,46} The topography of the malformation differs depending on the affected gene,⁸ suggesting that the gene products differ in function, location, or both. Other proteins, including neureglin and astrotactin, have been shown to regulate interactions between migrating neurons and radial glial cells^{69–71} in animal models, although the effects of mutations in humans are not known. Termination of neuronal migration has been linked to the extracellular protein reelin⁷² and the cytoplasmic protein mDab1,⁷³ which is believed to transduce signals generated by putative reelin receptors Apoer2 and Vldlr.^{74–76}

With the elimination of the diffuse versus focal/multifocal separation, Group II has also been simplified significantly. It is now divided into three main

Table 6 Classification of the cobblestone complex syndromes

II. Malformations due to abnormal neuronal migration

B. Cobblestone complex

1. Congenital muscular dystrophy syndromes
 - a. Walker–Warburg syndrome (WWS)
 - b. Muscle–eye–brain disease (MEB)
 - c. Fukuyama congenital muscular dystrophy (FCMD)
2. Syndromes with no involvement of muscle
 - a. Cobblestone complex MEB pattern with normal eyes and muscle
 - b. Cobblestone complex diffuse with normal eyes and muscle

categories, including the Lissencephalies, Cobblestone Complex, and Other Heterotopia (tables 2 and 5 through 7). The discovery that subcortical band heterotopia (SBH) comprises part of the classic lissencephaly spectrum and can result from less severe mutations of the *DCX* or *LIS1* genes resulted in moving SBH from the Other Heterotopia to the Lissencephalies category, which is now called the Lissencephaly/Subcortical Band Heterotopia Spectrum (see tables 1 and 3).^{3,45,47,48} Another consideration was to list classic lissencephaly (agyria–pachygyria–SBH) and possibly all of the lissencephalies as heterotopia syndromes, as the deep cellular layer of neurons arrested during migration to the cortex technically comprises a heterotopia. However, the pure heterotopia syndromes are very distinct from the lissencephaly syndromes by both clinical and imaging criteria. Ultimately, classifying SBH as part of the lissencephaly syndrome seemed more appropriate than classifying classic lissencephaly as a heterotopia syndrome. We have also added some newly identified disorders such as lissencephaly with cerebellar hypoplasia and lissencephaly with agenesis of the corpus callosum, which seem to be distinct enough to separate from the classic lissencephaly spectrum.⁷⁷⁻⁷⁹

We have intentionally avoided the use of the old

Table 7 Classification of heterotopia

II. Malformations due to abnormal neuronal migration

C. Heterotopia

1. Subependymal (periventricular) heterotopia
 - a. Periventricular nodular heterotopia (PNH)
 - i. Bilateral PNH with *FLN1* mutations
 - ii. Other PNH
 - iii. PNH with abnormal overlying cortex
 - b. Periventricular laminar/ribbon heterotopia
2. Subcortical heterotopia (other than band heterotopia)
 - a. Large subcortical heterotopia with abnormal cortex, hypogenetic corpus callosum
 - b. Single subcortical heterotopic nodule
 - c. Excessive single neurons in white matter
3. Marginal glioneuronal heterotopia

terms “type 1” and “type 2” lissencephaly, instead favoring the more descriptive terms of classic lissencephaly (or agyria–pachygyria–SBH; Group II.A) and cobblestone complex (Group II.B). As more and more types of lissencephaly have been found and described, identification by numbers became confusing, and some published reports used them incorrectly. Indeed, it was concluded that cobblestone complex should not be classified as one of the lissencephalies at all. While the brain surface is smooth in Walker–Warburg syndrome, it is not smooth in the other cobblestone complex syndromes such as muscle–eye–brain disease and Fukuyama congenital muscular dystrophy. In addition, the mechanism by which the cortical malformation develops is entirely different. In the true lissencephalies, many neurons fail to reach the cortical plate, whereas in the cobblestone cortex, many neurons move too far, migrating through a defective glial limiting membrane into the subpial space.^{29-32,80} These differences in both anatomy and mechanism justify classification of the cobblestone complex separately from the lissencephalies (see tables 2 and 6).

With the reclassification of SBH to the Lissencephaly category, heterotopia are divided into three major groups, including Subependymal, Subcortical, and Marginal Glioneuronal Heterotopia (see table 7). Two groups of subependymal (also called periventricular) heterotopia require comment. Recent publications^{81,82} have shown that one type of subependymal heterotopia, specifically multiple bilateral periventricular nodular heterotopia, may be familial, usually with an X-linked pattern of inheritance. It appears that unilateral subependymal heterotopia and sparsely scattered subependymal heterotopia (even if bilateral) are almost always sporadic¹⁴; no familial cases have as yet been reported. The second comment regards a series of patients observed by the authors with subependymal heterotopia that appear as linear or sinusoidal ribbons of heterotopic gray matter in contrast to the usual nodular morphology. It is not yet clear how these differ clinically or genetically from the more typical nodular form, but their imaging appearance is distinct enough to warrant placing them in a separate category.

Group III: Malformations due to abnormal late neuronal migration and cortical organization. The molecular mechanisms involved in cortical organization are those of neurite extension, synaptogenesis, and neuronal maturation. The molecular mechanisms of these steps are slowly being elucidated.^{83,84}

This revision again classifies polymicrogyria and schizencephaly together, under the Polymicrogyria/Schizencephaly Complex (Group III.A), as they are so often observed together in patients (table 8). Indeed, we are aware of no cases of schizencephaly without accompanying polymicrogyria (although the converse is clearly not true). In addition, both polymicrogyria and schizencephaly have been reported in the same family.⁸⁵ Moreover, recent laboratory work has reinforced our belief that polymicrogyria results

Table 8 Classification of the polymicrogyrias and schizencephalies

III. Malformations due to abnormal cortical organization (including later neuronal migration)
A. Polymicrogyria and schizencephaly
1. Bilateral polymicrogyria syndromes
a. Bilateral diffuse polymicrogyria (BDP)
b. Bilateral frontal polymicrogyria (BFP)
c. Bilateral perisylvian polymicrogyria (BPP)
i. Autosomal dominant (22q11.2 and others)
ii. Autosomal recessive
iii. X-linked
d. Bilateral parieto-occipital polymicrogyria
e. Bilateral mesial occipital polymicrogyria
2. Schizencephaly (polymicrogyria with clefts)
a. Isolated schizencephaly
b. Septo-optic dysplasia—schizencephaly syndrome
c. Other rare schizencephaly syndromes
3. Polymicrogyria with other brain malformations or abnormalities
a. Polymicrogyria with abnormal white matter
4. Polymicrogyria or schizencephaly as part of Multiple Congenital Anomaly/Mental Retardation syndromes
a. Adams–Oliver syndrome
b. Aicardi syndrome
c. Arima syndrome
d. Delleman syndrome (oculocerebrocutaneous syndrome)
e. Galloway–Mowat syndrome
f. Micro syndrome

from a developmental disorder or injury that occurs toward the end of the period of neuronal migration and the early phase of cortical organization.⁸⁶⁻⁸⁸

Since the first classification was published, several bilateral polymicrogyria syndromes (Group III.A.1¹⁹⁻²¹) have been described in addition to the well-known bilateral perisylvian form.⁸⁹ Also, many families have now been described in which multiple members have bilateral perisylvian polymicrogyria.^{25,27} Many of these pedigrees, and others reviewed by the authors, are consistent with X-linked inheritance, although some are compatible with autosomal dominant or autosomal recessive inheritance. Recent data also show a significant skewing of the sex ratio toward boys for bilateral perisylvian polymicrogyria (W.B. Dobyns, unpublished data). Perisylvian polymicrogyria (both unilateral and bilateral) has been found in several chromosomal aneuploidy syndromes, most prominently with deletion of the chromosome 22q11.2 DiGeorge syndrome critical region.^{22,49,50} Both polymicrogyria and schizencephaly may occur with prenatal cytomegalovirus infection and with vascular problems related to twinning. They have also been described in several multiple congenital anomaly–mental retardation syndromes including

Adams–Oliver, Arima, Galloway–Mowat, and Delleman syndromes. Polymicrogyria and schizencephaly thus appear to be common malformations, which may be caused by many different genetic and environmental causes, including in utero events.⁹⁰

As they cannot be differentiated by imaging, we do not separate unlayered from “four-layered” polymicrogyria in our classification. Some authors suggest that this is an important distinction, postulating that the unlayered form is the expression of impaired genetic programming whereas the four-layered form has characteristics more suggestive of a late disruption of cortical organization.⁹¹ Others point out, however, that the four-layered type of polymicrogyria is heterogeneous, with sometimes four cortical layers, sometimes three, and sometimes two peripheral to the cell-sparse layer,⁹²⁻⁹⁴ speculating on a possible continuum with the unlayered form. Laboratory models of polymicrogyria^{87,95} will, it is hoped, help to better clarify these issues.

Also, since our first classification was published, a study has been published suggesting that some cases of schizencephaly are caused by mutation of the *EMX2* gene.⁹⁶ However, this result has not been confirmed in follow-up studies by other authors. Moreover, a search for *EMX2* mutations in 15 patients with schizencephaly by one of the authors revealed no abnormalities (W.B. Dobyns, unpublished observations). Therefore, we have chosen not to include schizencephaly in table 1, preferring to wait until the association with *EMX2* mutations is confirmed.

The other listings under the heading of Malformations Secondary to Abnormal Cortical Organization are Cortical Dysplasia Without Balloon Cells (Group III.B) and Microdysgenesis (Group III.C). The authors all have experience with the former, which has a different imaging appearance from cortical dysplasia with balloon cells.⁹⁷⁻⁹⁹ Indeed, in our experience, these cortical dysplasias have the appearance of a localized prenatal cortical injury, suggesting that prenatal infarction or infection after neuronal migration might alter the local effects on cell maturation and result in the development of giant, dysplastic-appearing cells. As mentioned earlier, the absence of balloon cells suggests that the divergence from normal development occurs after the period of cell proliferation. The absence of heterotopia puts the timing after the period of neuronal migration, as well. As for microdysgenesis, some authors believe that it is an important developmental anomaly in many patients with epilepsy,^{100,101} whereas others dispute this.¹⁰² We merely include the entity and leave it to others to determine its importance.

Group IV: Malformations of cortical development, not otherwise classified. The major malformations in this class are those associated with metabolic, especially peroxisomal disorders, such as Zellweger syndrome. The cortex in Zellweger syndrome has been studied in detail.^{103,104} The cortical malformation is composed of gyri that are excessively numerous but still excessively broad with a shallow

amplitude, a condition that does not fit into any of the known categories of malformations. The term "pachymicrogyria" has been applied,¹⁰⁵ but we choose not to use this term, which seems to us an oxymoron. As the mechanism of the cortical malformation is unknown, we prefer to list it as unclassified. Other unclassified malformations such as sublobar dysplasia¹⁰⁶ should be listed here as well until their nature is better understood.

Discussion. This classification system has been established by physicians who are active in the everyday evaluation and care of children and adults with malformations of cortical development. Its purpose is to provide a useful and logical framework by which other physicians, involved in both clinical and research activities in this field, can classify their patients. It might be argued that this classification is too heavily weighted toward imaging and not enough toward pathology or genetics. We would respond that imaging data are available for essentially all patients, whereas pathologic material is available for very few. In addition, the imaging characteristics of many malformations have been well established, whereas the genetics and molecular biology are known for only a few of them. The classification uses genetic data to classify patients whenever they are available. For example, we have separated Tuberous Sclerosis into two categories (I.C.1.a.i and I.C.1.a.ii) because two separate genes have been identified that cause the disorder when mutated, despite the lack of any demonstrated pathologic or molecular biologic difference in the cortical tubers between the two groups and the absence of significant differences in imaging phenotype (TSC2 seems to have a more severe clinical phenotype).^{54,107,108} When genetic information is not available, however, imaging data seem the logical objective criteria to use for the classification at this time.

This classification might also be criticized for some of the assumptions that have been made in assigning malformations to certain categories. For example, one might question whether it is justifiable to classify Cortical Dysplasia Without Balloon Cells into Group III based on the fact that histopathology and imaging have the appearance of localized prenatal injury. Similarly, one might question whether Taylor-type cortical dysplasia, cortical tubers, and gangliocytoma, which are varied and strictly localized disorders, should all be grouped under the common denominator of Abnormal Cell Proliferation without proof from biologic models. To these potential criticisms, one must respond that any useful model is based on some assumptions. Indeed, Sarnat¹⁰⁹ uses a number of assumptions in assigning malformations to his molecular genetic classification. The authors do not claim that this version of the classification system is the last. Undoubtedly, new discoveries in the future will show that some of the disorders included in this classification should be reclassified into a new group. Some disorders that are

listed separately may have to be combined, whereas others that are listed as a single disorder may have to be divided into multiple groups. New disorders will need to be added. Indeed, even the framework of the classification will likely need modification as new features of cortical development are discovered. The strength of this classification system is that it has the flexibility to allow these changes in both its framework and its listings with periodic updates as new discoveries necessitate change.

Other classification schemes have been proposed.¹⁰⁹⁻¹¹¹ That of Mischel et al.¹¹¹ is based entirely on pathology, making it impractical and nearly impossible to apply to the vast majority of patients with malformations of cortical development who never undergo biopsy or resection. The suggested classification of Raymond et al.¹¹⁰ is based entirely on an epilepsy series and, as a result, omits the vast quantity of cortical malformations that are seen in children presenting with developmental delay, neonatal encephalopathy, or congenital motor dysfunction. The proposed classification of Sarnat¹⁰⁹ is based entirely on molecular genetics. The author argues that this type of classification avoids "lumping complex disorders with multiple etiologies . . . as if they were a single malformation."¹⁰⁹ We do not argue with the concept that the ideal classification separates malformations of different etiologies, even if they have similar appearances. We have also used genetic information whenever possible in our classification. However, molecular genetic data are not available for most of the malformations listed in our classification and likely will not be for some years. Therefore, both classifications will need periodic revisions. We would argue that the major difference between our classification and that of Sarnat is that we have chosen to list malformations based on their most likely biologic cause when the precise biologic cause is not known.

Close examination reveals that Sarnat's classification has many similarities to ours.¹ His Category V, Aberrations in Cell Lineages by Genetic Mutation, is very similar to our Category I. His Categories VI.A.1 and VI.A.2, Disorders of Secretory Molecules and Genes That Mediate Migrations, closely resemble our Category II, and his Category VI.A.3, Late Course of Neuroblast Migration/Architecture of Cortical Plate, closely resembles our Category III. However, by using clinical, pathologic, and radiologic information as well as molecular genetic information, our classification, with its more extensive listing of cortical malformations, is perhaps currently more useful to the clinician whose patient is diagnosed with one of these disorders.

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