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REVIEW ARTICLE

A developmental and genetic classification for midbrain-hindbrain malformations

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Advances in neuroimaging, developmental biology and molecular genetics have increased the understanding of developmental disorders affecting the midbrain and hindbrain, both as isolated anomalies and as part of larger malformation syndromes. However, the understanding of these malformations and their relationships with other malformations, within the central nervous system and in the rest of the body, remains limited. A new classification system is proposed, based wherever possible, upon embryology and genetics. Proposed categories include: (i) malformations secondary to early anteroposterior and dorsoventral patterning defects, or to misspecification of mid-hindbrain germinal zones; (ii) malformations associated with later generalized developmental disorders that significantly affect the brainstem and cerebellum (and have a pathogenesis that is at least partly understood); (iii) localized brain malformations that significantly affect the brain stem and cerebellum (pathogenesis partly or largely understood, includes local proliferation, cell specification, migration and axonal guidance); and (iv) combined hypoplasia and atrophy of putative prenatal onset degenerative disorders. Pertinent embryology is discussed and the classification is justified. This classification will prove useful for both physicians who diagnose and treat patients with these disorders and for clinical scientists who wish to understand better the perturbations of developmental processes that produce them. Importantly, both the classification and its framework remain flexible enough to be easily modified when new embryologic processes are described or new malformations discovered.

Keywords: cerebellum; brain stem; malformations; development

Abbreviations: CDG = congenital disorders of glycosylation; FOXC1 = Forkhead box C; GABA = gamma-aminobutyric acid; GPR = G protein-coupled receptor; JSRD = Joubert syndrome and related disorders; LCH = lissencephaly with cerebellar hypoplasia; MHB = midbrain-hindbrain boundary; OPHN = oligophrenin; PCH = pontocerebellar hypoplasias; Shh = sonic hedgehog signalling molecule

Introduction

Recent advances in developmental biology, molecular genetics and neuroimaging have led to an increased interest in and understanding of developmental disorders of the embryonic midbrain and hindbrain that grow into the adult brainstem and

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cerebellum. Malformations of the brainstem and cerebellum often occur as the only recognized malformation in individuals with mental retardation or autism (Soto-Ares *et al*., 2003; Courchesne *et al*., 2005). However, they have also been increasingly recognized in patients with malformations of the cerebrum such as lissencephaly (Ross *et al*., 2001; Poirier *et al*., 2007), cobblestone malformations (Aida *et al*., 1994; Barkovich, 1998; Triki *et al*., 2003; van Reeuwijk *et al*., 2006) or callosal anomalies (Barkovich *et al*., 2007); and in patients with developmental disorders of other organ systems such as the kidneys or skin (Brocks *et al*., 2000; Gleeson *et al*., 2004; Tan *et al*., 2005; Valente *et al*., 2005).

The number and complexity of recognized malformations of the brainstem and cerebellum has been steadily increasing. While the practical 'every day' approach to a patient with a midbrain-hindbrain malformation is still based mainly on the neuroimaging 'pattern recognition' approach, a system by which these disorders can be clearly identified and compared is badly needed. A few classification systems have been proposed (Patel and Barkovich, 2002; Parisi and Dobyns, 2003), but none are comprehensive or widely used. Here we take advantage of a combination of large clinical practices and an expanding knowledge base regarding neuroembryology and developmental biology, structural imaging and molecular genetics to present a comprehensive, yet flexible, system of classification for these collectively common disorders.

This classification system (Table 1) relies most heavily on embryology and genetics, as these comprise the bodies of knowledge that most easily allow relationships among a large group of disorders to be clarified. A similar classification system for malformations of cortical development (Barkovich *et al*., 2005) has proven useful for both physicians who diagnose and treat patients with these disorders and for clinical scientists who wish to understand better the perturbations of developmental processes that produce them. Importantly, both the classification and its framework remain flexible enough to be easily modified when new embryologic processes are described or new malformations discovered (Barkovich *et al*., 2005).

Overview of midbrain and hindbrain development

The central nervous system derives from the dorsal epiblast of the vertebrate embryo, and is induced by a combination of signals originating in the region of Hensen's node at the posterior margin of the early embryo (Wurst and Bally-Cuif, 2001). After many steps, a neural tube is formed that subsequently develops a series of vesicles at its anterior (rostral) end. These three vesicles are designated the prosencephalon or forebrain (which soon divides into diencephalon and telencephalon), the mesencephalon (midbrain), and the rhombencephalon (hindbrain), which divides into the rostral metencephalon (pons and cerebellum) and caudal myelencephalon (medulla oblongata). This differentiation along the anteroposterior axis (also called the rostral-caudal axis) is called patterning, a name given to the early differentiation of the neural tube (Lumsden and Krumlauf, 1996).

Table 1 **Overview of developmental and genetic classification of mid-hindbrain malformations**

- I. Malformations secondary to early anteroposterior and dorsoventral patterning defects, or to misspecification of mid-hindbrain germinal zones
  - A. Anteroposterior patterning defects
    - 1. Gain, loss or transformation of the diencephalon and midbrain
    - 2. Gain, loss or transformation of the midbrain and rhombomere 1
    - 3. Gain, loss or transformation of lower hindbrain structures
  - B. Dorsoventral patterning defects
    - 1. Defects of alar and basal ventricular zones
    - 2. Defects of alar ventricular zones only
    - 3. Defects of basal ventricular zones only
- II. Malformations associated with later generalized developmental disorders that significantly affect the brainstem and cerebellum (and have pathogenesis at least partly understood)
  - A. Developmental encephalopathies associated with mid-hindbrain malformations
  - B. Mesenchymal-neurepithelial signalling defects associated with mid-hindbrain malformations
  - C. Malformations of neuronal and glial proliferation that prominently affect the brainstem and cerebellum
  - D. Malformation of neuronal migration that prominently affect the brainstem and cerebellum
    - 1. Lissencephaly with cerebellar hypoplasia
    - 2. Neuronal heterotopia with prominent brainstem and cerebellar hypoplasia
    - 3. Polymicrogyria with cerebellar hypoplasia
    - 4. Malformations with basement membrane and neuronal migration deficits
  - E. Diffuse molar tooth type dysplasias associated with defects in ciliary proteins
    - 1. Syndromes affecting the brain with low frequency involvement of the retina and kidney
    - 2. Syndromes affecting the brain, eyes, kidneys, liver and variable other systems
- III. Localized brain malformations that significantly affect the brainstem and cerebellum (pathogenesis partly or largely understood, includes local proliferation, cell specification, migration and axonal guidance)
  - A. Multiple levels of mid-hindbrain
  - B. Midbrain malformations
  - C. Malformations of rhombomere 1 including cerebellar malformations
  - D. Pons malformations
  - E. Medulla malformations
- IV. Combined hypoplasia and atrophy in putative prenatal onset degenerative disorders
  - A. Pontocerebellar hypoplasia
  - B. Mid-hindbrain malformations with congenital disorders of glycosylation
  - C. Other metabolic disorders with cerebellar or brainstem hypoplasia or disruption
  - D. Cerebellar hemisphere hypoplasia (rare, more commonly acquired than genetic, often associated with clefts or cortical malformation)

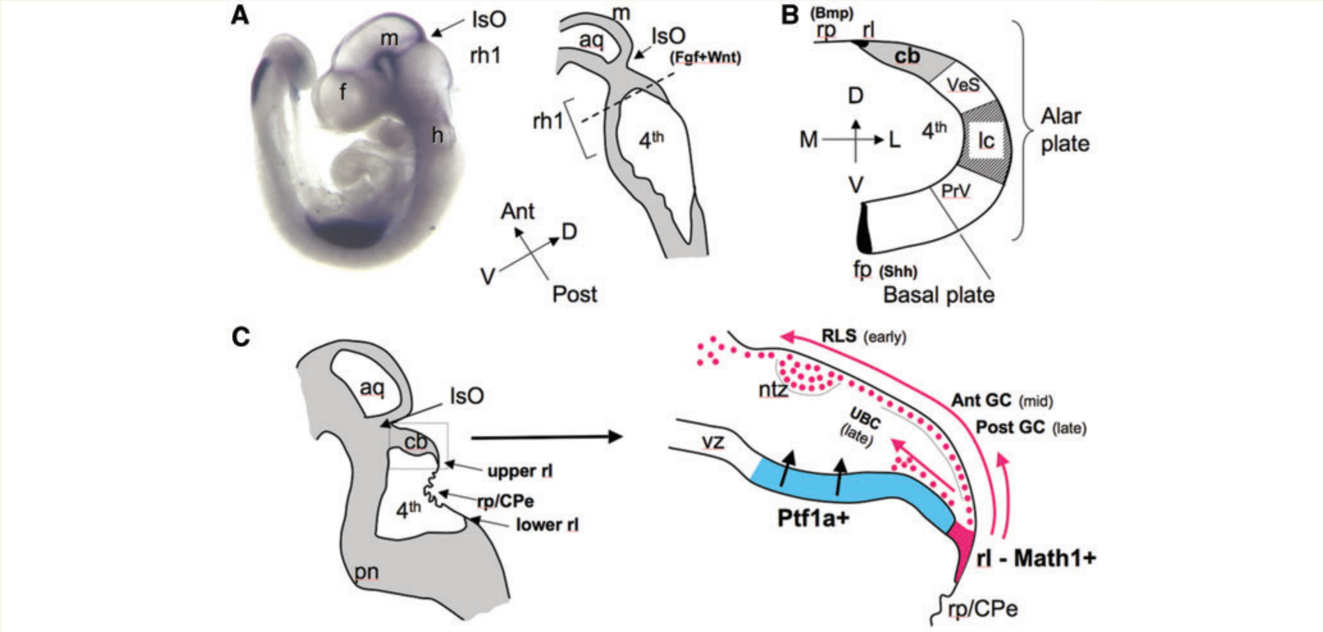

Figure 1 Mid-hindbrain embryonic development. (**A**) Early neural tube development—e9.5 mouse embryo stained for Lmx1b expression—a transcription factor expressed in many places of the embryo including the isthmic organizer (IsO) a signalling center at the midbrain (m) hindbrain (h) boundary adjacent to hindbrain rhombomere 1 (rh 1). The isthmic organizer secretes fibroblast growth factor (Fgf) and Wnt proteins which provide regional identity and pattern proliferation along the anterior/posterior axis. To the right is a schematic parasagittal section through the mid/hindbrain region. Arrows indicate anterior/posterior (A/P) and dorsal/ventral (D/V) axes. f = forebrain; aq = aqueduct; 4^{th} = fourth ventricle. (**B**) Distinct progenitor domains along the dorsal/ventral axis of rhombomere 1 give rise to distinct structures. A schematic diagram of a hemi-transverse section through rhombomere 1 (indicated by dashed line in A). The cerebellum is derived from the dorsal-most domain of rhombomere 1 alar plate, adjacent to the rhombic lip (rl) and dorsal roof plate (rp). The roof plate secretes bone morphogenic protein (Bmp) and Wnt proteins which pattern dorsal cell fate and proliferation. Fate mapping experiments in chick/quail chimeras have demonstrated that other alar derived structures include the superior vestibular nucleus (VeS) and principle trigeminal sensory nucleus (PrV). The locus coerulus (lc) is also an alar plate rhombomere 1 derivative, although its progenitors migrate tangentially to settle eventually in the basal plate. The basal plate also has multiple derivatives, including the raphe nucleus (not shown), which is patterned by the influence of Shh protein secreted from the floor plate (fp). Arrows indicate dorsal/ventral (D/V) and medial lateral (M/L) axes. (**C**) Within the cerebellar anlage, distinct progenitors give rise to glutamtergic versus GABAergic neurons. Schematic parasagittal section through the mid/hindbrain region of a mouse e12.5 neural tube. Pontine flexure has rearranged the previously A/P oriented cerebellar anlage relative to the brainstem and developing pontine nucleus (pn). Within the developing cerebellar anlage two distinct progenitor zones form marked by distinct transcription factors, Math1 and Ptf1a. Math1 expression in the rhombic lip (rl) was induced by bone morphogenic protein signalling from the roof plate (rp) which itself is differentiating into the choroid plexus (CPe). Math1+ rhombic lip progenitor cells give rise to multiple glutamaterigic+ derivatives in a time-dependent sequence. Early progenitors feed into the rostral migratory stream (RLS). The rostral migratory stream migrates over the cerebellar anlage and gives rise to multiple brain stem precerebellar nuclei, including the pontine nuclei. Rostral migratory stream cells next give rise to glutamategic deep cerebellar nuclei which settle into the nuclear transitory zone (ntz). Math1+ rhombic lip cells also generate cerebellar granule cells (GC) which form the cerebellar external granule layer in a anterior to posterior temporal gradient. Unipolar brush cells (UBC) are the final Math1+ rhombic lip population and migrate through the cerebellar while matter. Concurrently, the ventricular zone (vz) of the cerebellar anlage expresses Ptf1a. These progenitors exit the cell cycle, migrate radially into the cerebellar anlage and give rise to all GABAergic cerebellar cells, including Purkinje cells, GABAergic DCN and interneurons including Basket and Stellate cells.

The mechanisms that result in early anteroposterior patterning are partially understood (Chambers *et al*., 2009) and, other than the formation of the diencephalic-mesencephalic boundary and the midbrain-hindbrain boundary (MHB), are beyond the scope of this manuscript. In murine and chick models, the diencephalic-mesencephalic boundary appears to form, at least in part, from interactions between the *Pax6*, *Pax2*, *En1* and *En2* genes. *Pax6* confers diencephalic fate by repressing both *Pax2* and *En1*, while *En1* represses *Pax6* expression in the mesencephalon (Lim and Golden, 2007). Changes in expression of these genes will shift the diencephalic-mesencephalic boundary caudally (more *Pax6*) or rostrally (more *Pax2*/*En1*). Similarly, the location of the MHB is determined by the expression of *Otx2* in the caudal midbrain and *Gbx2* in the rostral hindbrain; increase or posterior shifts in the expression of *Otx2* or decrease in *Gbx2* shift the MHB caudally, while decrease in *Otx2* or increase or anterior shift in *Gbx2* shifts the MHB rostrally (Nakamura *et al*., 2005). The interaction of *Otx2* and *Gbx2* also specifies the location of the isthmus organizer (Fig. 1), a critical structure located at the MHB that functions via secreted Wnt and fibroblast growth factor signalling molecules to organize expression of genes and specify cell type (Broccoli *et al*., 1999; Wurst and Bally-Cuif, 2001): it is essential for normal brainstem and cerebellar development (Sotelo, 2004).

At the same time that anteroposterior patterning is taking place, an analogous process is occurring along the dorsoventral axis (Fig. 1). Dorsoventral patterning depends on the relative amounts of dorsalizing and ventralizing factors. The most important dorsalizing factors are proteins belonging to the bone morphogenic protein family that are produced by the non-neural ectoderm of the roof plate, while the most important ventralizing factor is sonic hedgehog (Shh) a signalling molecule that emanates from the prechordal plate and floor plate (Tanabe and Jessell, 1996; Wurst and Bally-Cuif, 2001). Along the dorsoventral axis, the mesencephalon is divided into the tegmentum (ventral region) and tectum (dorsal region) while the rostral hindbrain is divided into the pons (ventral region) and the cerebellum (dorsal region). The neuronal subtypes produced in these regions are specified by expression of local *Hox* genes and other transcription factors (Gaufo *et al*., 2004) and their targets (Chambers *et al*., 2009), as well as graded doses of signalling molecules, such as Shh and bone morphogenic protein from the floor and roof plates (Wurst and Bally-Cuif, 2001), all influenced by local organizers especially the isthmic organizer (Fig. 1) (Ye *et al*., 1998; Chizhikov *et al*., 2006*b*; Canning *et al*., 2007).

Although several of the genes involved in generation of mid- and hindbrain neurons have been discovered (Wang and Zoghbi, 2001; Wang *et al*., 2005; Sieber *et al*., 2007), the forces controlling neuronal progenitor proliferation are not as well understood as the timing and location of the proliferation. Many neurons in the posterior fossa are generated in the ventricular zone of the hindbrain, while far more are generated in the rhombic lips, the dorsalmost portion of the hindbrain proliferative neuroepithelium (Fig 1B) (Wingate and Hatten, 1999; Sotelo, 2004). The rhombic lips are separated into the upper (cerebellar) rhombic lip, located at the level of rhombomere 1, and the lower (hindbrain) rhombic lip, located at rhombomeres 2–8 (Fig. 1C) (Landsberg *et al*., 2005). Some of the neurons produced in the ventricular zone, such as the cerebellar Purkinje cells and other gamma-aminobutyric acid (GABA)-ergic cerebellar neurons, migrate radially in a relatively straightforward manner to their final location (Wang and Zoghbi, 2001). Many rhombic lip derivatives, however, such as the cerebellar granule cells and the so-called ‘precerebellar nuclei’ of the brain stem (i.e. inferior olive, lateral reticular and external cuneate nuclei) migrate along complex pathways, often tangential to the radial neuraxis and sometimes over considerable distances, guided by adhesion molecules, neurotrophins, and repulsive molecules that may be on the surface of cells or in the interstitium (Bourrat and Sotelo, 1990; Wingate and Hatten, 1999; Sotelo, 2004; Bloch-Gallego *et al*., 2005; Kawauchi *et al*., 2006; Yamada *et al*., 2007). Of interest, specific cell types seem to originate from distinct neuroepithelial domains (Fig. 1C). For example, *Ptf1a+* domains generate the GABAergic cerebellar Purkinje cells and mossy fibre neurons of the pontine nuclei, lateral reticular nuclei, and external cuneate nuclei (Bermingham *et al*., 2001), whereas *Atoh1+* (also called *Math1)* domains produce the glutamatergic cerebellar granule cells and climbing fiber neurons of the inferior olivary nuclei (Yamada *et al*., 2007). It was accepted for many years that deep cerebellar nuclear projection neurons (from the dentate, fastigial, globiform, and emboliform nuclei) are produced in the ventricular zone along with Purkinje cells (for review, see Wang and Zoghbi, 2001), migrating first outward to form a nuclear transitory zone, where they start to differentiate, and then entering a phase of inward migration that takes them to their ultimate position (Altman and Bayer, 1978; 1985). However, recent work suggests that glutamatergic deep cerebellar nuclear projection neurons arise from the rhombic lip, and then migrate rostrally in a subpial stream to the nuclear transitory zone (Fig. 1C) (Wang *et al*., 2005; Fink *et al*., 2006). Moreover, recent analysis suggests that all glutamatergic cerebellar neurons (deep nuclear projection neurons, in addition to granule cells, and unipolar brush cells) are produced in the rhombic lips, whereas all GABAergic cerebellar neurons (Purkinje cells and inhibitory interneurons) are produced in the cerebellar ventricular zone (Englund *et al*., 2006; Fink *et al*., 2006).

As in the cerebrum, the final destination of migrating neurons in the developing cerebellar cortex, and their specific neuronal cell fate, depend upon many factors: (i) genetic programming; (ii) disengagement signals at the end of migration; (iii) molecular signals received from the surrounding cellular milieu after termination of migration; and (iv) the establishment of distant and local axonal connections (Sotelo, 2004; Chizhikov *et al*., 2006*b*; Englund *et al*., 2006; Kawauchi *et al*., 2006; Leto *et al*., 2006; Porcionatto, 2006; Weisheit *et al*., 2006). The later parts of this process, including final positioning within the cortex, development of (axons and) dendrites and synapses, and other changes to form a functionally mature neuron, are termed ‘cortical organization’; this process probably begins during neuronal migration, as the distances are shorter and the pathfinding easier in the less mature brain. Axons of the same pathways can later navigate more simply, by detecting signals emanating from these pioneer axons, a process known as fasciculation (Tessier-Lavigne and Goodman, 1996). As for neuronal migration, pathway selection by axons is oriented by a large variety of short and long range guidance cues distributed along the entire pathway, to which different axons respond differently (Richards *et al*., 2004). Indeed, the growth cone on the leading process of a migrating neuron in many ways resembles that of a pathfinding axon and the mechanisms of pathfinding are likely to be similar (Hatten, 2002; Gomez and Zheng, 2006; Round and Stein, 2007). Neurons of brain stem nuclei also migrate to their final location. With the exception of the oculomotor (third nerve) nuclei, which derive from the mesencephalon, cranial nerve nuclei are derived from rhombencephalic (hindbrain) neuronal precursors: the fourth nerve from rhombomere 1, fifth nerve from rhombomeres 2–3, sixth nerve from rhombomeres 5–6, and seventh nerve from rhombomeres 4–5 (Trabousli, 2004). Due to their compartmental identity, the neuronal progenitors display programmed migratory behaviors and send axons along defined trajectories to their peripheral targets. While the position of the neural cell progenitors along the anteroposterior axis determines the identity of the nucleus, its sensory or motor function is determined by its position along the dorsoventral axis. Graded expression of *Shh*, together with *Pax6* and *Nkx.2.2*, along the dorsoventral axis appears to generate domains conducive to either motor (ventral) or sensory (dorsal) cell fate

(Trabousli, 2004). Downstream cell fate decisions are regulated by yet other genes. For example, the paired-like homeodomain protein Phox2b is required for the formation of all branchial and visceral, but not somatic, motor neurons in the hindbrain (Pattyn *et al*., 2000*b*). Mice lacking *Phox2b* have early disruption of motor neuron differentiation, with precursors dying in the neuroepithelium or not switching on postmitotic markers that allow later differentiation (Pattyn *et al*., 2000*b*). The last stages of cortical organization continue into the postnatal period; indeed, the last migrations of granule cells from the transient external granular layer into the definitive granular layer of the cerebellar cortex do not occur until the middle of the second postnatal year in humans (Donkelaar *et al*., 2003). Therefore, a greater overlap of the migration and cortical organization phases occurs in the cerebellum than in the cerebrum, and some anomalies of the cerebellar cortex may develop quite late in gestation or even, possibly, after birth. From a conceptual point of view, it is useful to keep these two phases of cerebellar development separate even though they are not (yet) separated in the classification system.

Framework of the classification

In constructing this classification, we used known embryologic, genetic, imaging, and pathophysiologic information from the literature plus information acquired from our own patients and laboratory work. Whenever the genetics/embryology of the disorder was well enough understood, we have classified disorders primarily by genotype (ultimately, we would hope that the entire classification will be arranged this way); when the genetics/embryology was incomplete, we classified by clinico-radiologic phenotype. Recognizing that humans have differences from other animals in all of these areas, we have specified when using chick, murine, or zebra fish-derived data in both our tables and in the text. The first step was to use fundamental embryology in order to separate localized MHB malformations due to early defects in anteroposterior and dorsoventral patterning or mis-specification of cell proliferation zones in the MHB, from malformations that result from later events such as axonal pathfinding and neuronal migration (or disruptions). We next considered existing knowledge regarding MHB malformations associated with more widespread developmental disorders affecting forebrain structures and those restricted to regions derived from the midbrain or hindbrain; we separated these two large groups and then classified them according to the underlying processes involved. When the associated genes and proteins, or their functions, were known, this information was included and used as part of the classification process. Recognizing that we have only limited knowledge regarding the pathogenesis of many brainstem and cerebellar malformations, among which are some of the most common and best known, the malformations were classified in the most likely category according to our current knowledge. The flexibility of the system allows the disorders to be reclassified as our knowledge of underlying genetics and embryology progresses. This leaves a few rare disorders with evidence for both prenatal origin and disease progression, which we place in the last group. On the basis of these considerations, we propose to separate midbrain-hindbrain malformations into the following four major groups.

(i) Malformations secondary to early anteroposterior and dorsoventral patterning defects, or to misspecification of mid-hindbrain germinal zones.
(ii) Malformations associated with later generalized developmental disorders that significantly affect the brainstem and cerebellum (and have a pathogenesis that is at least partly understood).
(iii) Localized brain malformations that significantly affect the brain stem and cerebellum (pathogenesis partly or largely understood, includes local proliferation, migration and axonal guidance).
(iv) Combined hypoplasia and atrophy in putative prenatal onset degenerative disorders.

These groups will form the framework of the new classification and, wherever possible, will contain those disorders known, or expected to, result from developmental aberrations during a particular process. These groups differ substantially from those used in previously proposed classifications of cerebellar malformations (including ours), which were largely based on the anatomic regions involved (Parisi and Dobyns, 2003) or the end result morphologic appearance of the malformation (Patel and Barkovich, 2002). They also differ from classifications of cortical malformations based on embryology and genetics (Barkovich *et al*., 2005), largely because the embryology of the midbrain and hindbrain, and the morphologic consequences of disturbing the normal embryologic processes, are currently not as well defined. As with previous classifications based on embryology and genetics, this classification integrates previous and novel findings, provides a comprehensive view of all major midbrain and hindbrain structures, and has the possibility to expand to accommodate new discoveries. Additional strengths of this system are its flexibility and the understanding it renders to those using it. There is flexibility both in the framework of the classification and in the distribution of malformations within each group: either can be changed as our knowledge of the malformation, its cause, or of the processes involved in midbrain-hindbrain development, change. Ultimately, as in a similar genetic/embryologic classification of malformations of cortical development (Barkovich *et al*., 2005), we expect that this classification will evolve into a system that almost exclusively uses embryology and genetics as the bases for classification, with clinical phenotypes as subcategories listed under the major categories that are the causative genes and the pathways or networks in which their protein products participate.

Justification of classification

Group I. Malformations secondary to early patterning defects

Malformations secondary to early patterning defects include those with abnormalities of anteroposterior or dorsoventral segmentation of the brainstem (Table 2), and are often associated with

Table 2 **Group I. Malformations secondary to early anteroposterior and dorsoventral patterning defects, or to misspecification of mid-hindbrain germinal zones**

Defects	Examples	Comments and references
Early patterning defects		
I.A. Mid-hindbrain antero posterior patterning defects		These are predominately anteroposterior defects, but may have associated dorsoventral defects
I.A.1 Gain, loss or transformation of the diencephalon and midbrain		This group is meant to include malformations associated with putative diencephalic–mesencephalic organizer disruption
I.A.1.a. Gain of diencephalon or gain of midbrain	Human • Enlarged midbrain with midline dorsoventral hyperintensity	(Barkovich *et al*., 2007)
I.A.1.b. Loss of diencephalon or loss of midbrain	Human • Short midbrain with normal cerebellum	(Barkovich *et al*., 2007)
I.A.1.c. Gain of diencephalon and loss of midbrain	Zebrafish mutants • *zPbx1-mo* (morpholino knockdown) has gain of diencephalon and loss of midbrain	(Ericson *et al*., 1997)
	Human • Short thick midbrain with 3V extending into midbrain	Barkovich, unpublished data
I.A.1.d. Loss of diencephalon and gain of midbrain	Human • Elongated midbrain with normal cerebellum • Cleft midbrain	(Barkovich *et al*., 2007)
I.A.2. Gain, loss or transformation of the midbrain and rhombomere		This group is intended to include malformations associated with disruption of the isthmic organizer. Rhombomere 1 develops into portions of the pons and the entire cerebellum
I.A.2.a. Gain of midbrain or gain of rhombomere 1	Human • See 1a1a	We cannot differentiate between diencephalic–mesencephalic organizer and isthmic organizer disruptions in isolated gain of midbrain
I.A.2.b. Loss of midbrain or loss of rhombomere 1	Mouse mutants • Wnt1$^{-/-}$ • fibroblast growth factor$^{cko/cko}$ • En1$^{-/-}$	(Wurst and Bally-Cuif, 2001)
	» All three have deletion of posterior midbrain, vermis and most of cerebellum hemispheres Human • Brainstem disconnection, mesencepalic-pontine	(Poretti *et al*., 2007*b*)
I.A.2.c. Gain of midbrain and loss of rhombomere 1	Mouse mutant • Gbx2$^{-/-}$ with elongated midbrain, small pons-cerebellum Human • Giant midbrain-absent vermis in OCCS • Giant midbrain-absent vermis (isolated)	(Millet *et al*., 1999; Moog *et al*., 2005; Barkovich *et al*., 2007)
I.A.2.d. Loss of midbrain and gain of rhombomere 1	Mouse mutants • Otx2$^{-/-}$ with short midbrain, long pons-cerebellum Human • Short midbrain with long pons and enlarged anterior vermis	(Broccoli *et al*., 1999; Barkovich *et al*., 2007)
I.A.3. Gain, loss or transformation of lower hindbrain structures		These structures are derived from hindbrain segments rhombomeres 2–7; the cerebellum should be less or not involved
I.A.3.a. Gain of pons or medulla	No good examples	We are looking for examples of elongated pons or medulla in humans
I.A.3.b. Loss of pons or medulla	Human • Brainstem disconnection, pontomedullary	(Poretti *et al*., 2007*b*)

(continued)

Table 2 Continued

Defects	Examples	Comments and references
I.A.3.c. Mixed gains and losses of pons or medulla	Mouse mutants • Krox20$^{-/-}$ with transformation of rhombomere 3 to rhombomeres 2/4 and rhombomeres 5 to rhombomeres 6 identities Human • Short pons – long medulla malformation, some with ventral or dorsal midbrain clefts • Enlarged 'pons-like' medulla	(Schneider-Maunoury *et al*., 1993; Barkovich *et al*., 2007)
I.A.3.d. Segmental shifts (A>P or P>A) of pons or medulla	Mouse mutants • Hoxa1$^{-/-}$ • Hoxb1$^{-/-}$ • Hoxb2$^{-/-}$ • Hoxa1$^{-/-}$; Hoxb1$^{-/-}$; Hoxb2$^{-/-}$ triple mutants » These single, double and triple mutants have defects of hindbrain segments rhombomeres 4–6 Human by genotype • HOXA1$^{+/-}$ » Athabaskan brainstem dysgenesis syndrome » Bosley-Salih-Alorainy syndrome	Human HOXA1 mutations are associated with horizontal gaze abnormalities, hearing loss, facial weakness, hypoventilation, mental retardation and autism spectrum disorder (Gavalas *et al*., 1998, 2003; Studer *et al*., 1998, 2003; Tischfield *et al*., 2005; Bosley *et al*., 2008)
I.B. Mid-hindbrain dorsoventral patterning defects		Dorsoventral developmental defects mostly involving progenitor specification and proliferation
I.B.1 Defects of alar and basal ventricular zones		
I.B.1.a. Alar and basal ventricular zone defects involving all or uncharacterized dorsoventral sub-regions	Mouse mutants and humans • Probably any widely expressed ventricular zone gene	Disorders in this category will probably cause widespread CNS defects
I.B.2. Defects of alar ventricular zone only		Most known mutations affect multiple levels, but are best known in Rhombomere 1
I.B.2.a. Alar defects involving more than one dorsoventral sub-region	Mouse • Lbx1$^{-/-}$ Human by phenotype • Cerebellum agenesis with near normal development • Rhombencephalosynapsis • Gomez-Lopez-Hernandez syndrome	We have placed human rhombencephalosynapsis in this group with some uncertainty. (Michaud *et al*., 1982; Schachenmayr and Friede 1982; Romanengo *et al*., 1997; Takanashi *et al*., 1999; Brocks *et al*., 2000; Toelle *et al*., 2002; Moog *et al*., 2005; Pascual-Castroviejo *et al*., 2005; Sieber *et al*., 2007; Schell-Apacik *et al*., 2008)
I.B.2.b. Alar ventricular zone defects involving roof plate and rhombic lip derivatives including cerebellum granule cells, pontine nuclei, other cell types, choroid plexus	Mouse mutants • Atoh1$^{-/-}$ (Math1$^{-/-}$) • Lmx1a$^{-/-}$ • Itgb1$^{-/-}$ in CNS only Human • Diffuse granule cell hypoplasia of cerebellum*	*This very old classification may correspond to the congenital disorders of glycosylation type 1a, which would be moved to group II.G.2. (Pascual-Castroviejo *et al*., 2006). (Ben-Arie *et al*., 1997; Millonig *et al*., 2000; Blaess *et al*., 2004; Wang *et al*., 2005; Chizhikov *et al*., 2006*a*)
I.B.2.c. Alar ventricular zone defects involving the cerebellum ventricular zone including cerebellum GABAergic neurons, inferior olives, other cell types	Mouse mutants • Ptf1a$^{-/-}$ Human by genotype • PTF1A$^{-/-}$ » Pancreatic and cerebellar agenesis	(Hoveyda *et al*., 1999; Sellick *et al*., 2004; Glasgow *et al*., 2005; Hoshino *et al*., 2005)
I.B.2.d. Ventral alar ventricular zone defects involving multiple brainstem nuclei such as sensory cranial nerves, locus ceruleus (no cerebellum cells)	Mouse mutants • Phox2b$^{-/-}$ Human by genotype • PHOX2B$^{+/-}$ » Congenital central hypoventilation syndrome	(Pattyn *et al*., 2000*a*; Amiel *et al*., 2003; Weese-Mayer *et al*., 2003; Cross *et al*., 2004; Bachetti *et al*., 2005)
I.B.3. Defects of basal ventricular zone only		
I.B.3.a. Basal ventricular zone defects involving more than one dorsoventral sub-region	Mouse mutants • Shh$^{-/-}$	(Ericson *et al*., 1995, 1997)
I.B.3.b. Basal ventricular zone defects involving specific cranial motor nuclei	Human by phenotype • Duane retraction syndrome (cranial nerve VI)	Also see 1.A.3.d. Segmental shifts of pons or medulla, which underlie some examples in mouse. For example, loss of mouse *Hoxb1*

(continued)

Table 2 Continued

Defects	Examples	Comments and references
	» AD locus 8q13 • Hereditary congenital facial paresis (VII only) » AD loci 3q21–q22, 10q21.3–q22.1 • Moebius syndrome (VI and VII) » AD locus 13q12.2–q13	causes causes loss of the rhombomere 4-derived VIIth (facial) motor nerve This in turn causes paralysis of the muscles of facial expression, similar to the pathology of Bell's palsy or Moebius syndrome (Goddard *et al*., 1996). The human brain phenotypes have been limited to defects of brainstem structures, although experience remains limited. (Ziter *et al*., 1977; Slee *et al*., 1991; Nakano *et al*., 2001; Al-Baradie *et al*., 2002; Kohlhase *et al*., 2002, 2005; Holve *et al*., 2003; Bosley *et al*., 2006; Michielse *et al*., 2006; Sakaki-Yumoto *et al*., 2006; Engle *et al*., 2007; Miyake *et al*., 2008)

cerebellar anomalies. Malformations isolated to the cerebellum are not included here, as (in concept) the malformations in this group involve processes that predate formation of the cerebellar anlage. Malformations of this type are well known in animal models, and have been suspected in humans. However, techniques of brain imaging have only recently advanced to a point where thin section, high resolution volumetric data can be acquired in clinically feasible time slots. This has allowed high quality images of the brainstem to be produced in multiple planes and greatly facilitates the identification of morphologic abnormalities. In addition, improvements in diffusion tensor imaging have allowed production of colour fractional anisotropy maps of the brain stem, giving information about the morphology and location of the larger axonal pathways (Sicotte *et al*., 2006; Widjaja *et al*., 2006; Jissendi-Tchofo *et al*., 2009). With the advantage of these tools, malformations are more easily identified; many were reviewed in a recent publication (Barkovich *et al*., 2007).

The first subgroup of Group I is composed of disorders of anteroposterior segmentation, in which there is gain, loss, or transformation of segments at boundaries between sections of the neural tube, such as the diencephalic-midbrain boundary (Group I.A.1) or midbrain-rhombomere 1 boundary (Group I.A.2). For example, the combination of a shortened midbrain and enlarged pons associated with enlarged anterior vermis (Fig. 2) presumably results from either loss of midbrain, gain of rhombomere 1, or both. Similar rostral displacement of the MHB results from increased *Gbx2* expression or reduced *Otx2* expression in mouse and chick models (Nakamura and Watanabe, 2005; Waters and Lewandoski 2006), producing an enlarged rhombomere 1, especially anteriorly, and consequently an enlarged anterior vermis (Sgaier *et al*., 2005). Elongation of the medulla with shortening of the pons (Fig. 3) is postulated to result from mixed gains and losses of pons or medulla (I.A.3.c) or a segmental shift (I.A.3.d). Similar abnormalities result from murine embryo exposure to retinoic acid, which causes a dose-dependent anterior to posterior transformation of cell fate in which the hindbrain is expanded at the expense of the midbrain and forebrain (Lumsden, 2004). Lesser changes in retinoic acid gradient or other regionalizing molecules could result in transformations of the middle rhombomeres from pontine to medullary fate.

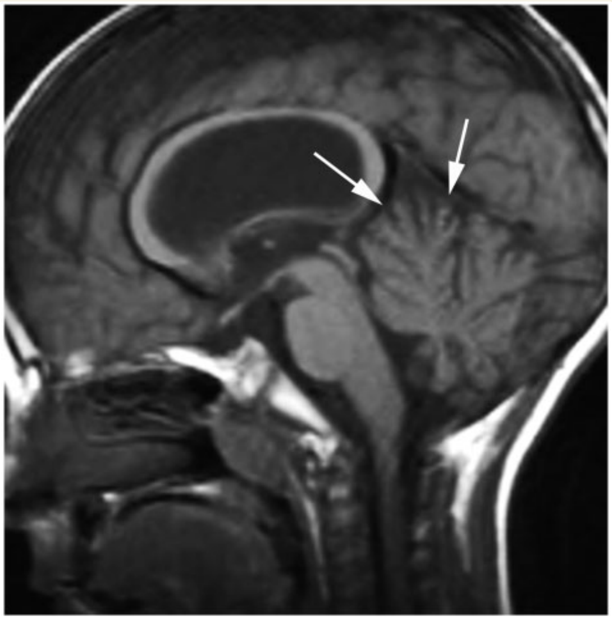

Figure 2 Defect of anteroposterior patterning. Sagittal T_1-weighted magnetic resonance image shows a short midbrain and elongated pons. Note the enlarged superior cerebellar vermis (arrows). These findings suggest alteration of caudal mesencephalon to rostral rhombencephalon, an anterior to posterior transformation, or rostral displacement of the midbrain-hindbrain boundary due to increased *Gbx2* expression or reduced *Otx2* expression.

The authors have observed several malformations in humans that suggest a posterior to anterior transformation at the diencephalon-mesencephalon junction. Shortening and thickening of the midbrain with midline (mesencephalic) cleft has been described as a malformation of unknown cause (Barkovich *et al*., 2007). But close inspection of imaging studies shows extension of the third ventricle and other diencephalic features into the upper part of the thickened midbrain (Fig. 4). This is interpreted as a putative posterior to anterior transformation of mesencephalon into diencephalon that results in caudal expansion of the diencephalon (I.A.1.c). A similar malformation has been described in mouse

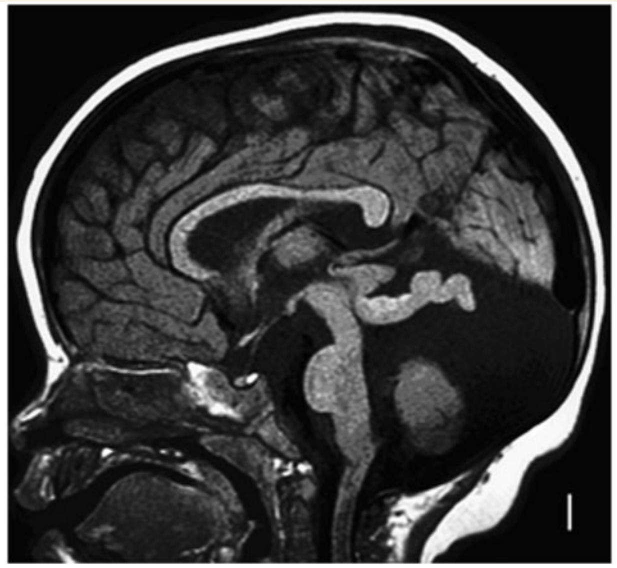

Figure 3 Elongation of the medulla with shortening of the pons. Sagittal T_1-weighted image shows a long midbrain and shortened pons. The tectum is dysmorphic and the cerebellum is dysmorphic and small. These findings suggest alteration of rostral rhombencephalon to caudal mesencephalon, a posterior to anterior transformation, with caudal displacement of the midbrain-hindbrain boundary due to decreased *Gbx2* expression or increased *Otx2* expression.

models with overexpression of *Pax6* in the diencephalon and underexpression of *En1/Pax2* in the anterior mesencephalon (Nakamura and Watanabe, 2005; Lim and Golden, 2007). Other patients have been described with elongated midbrain and medulla with short pons (Barkovich *et al*., 2007); classification is difficult in such cases. Further understanding of such patients awaits identification of genes and animal models.

Defects in dorsoventral patterning are herein postulated to result in abnormal development or function of specific mid-hindbrain ventricular zones and structures derived from them, including abnormal formation of brain stem nuclei, cranial nerves, or any cerebellar structures (Section I.B). For example, abnormal development of the superior rhombic lip may cause diffuse granule cell hypoplasia (Group I.B.2.b) while abnormal development of the cerebellar ventricular zone due to mutation of the *PTF1A* gene causes cerebellar (and pancreatic) agenesis (Group I.B.2.c) (Sellick *et al*., 2004; Hoshino *et al*., 2005) and defects of the basal ventricular zone result in defects of specific cranial nerve nuclei such as the abducens and facial nerves (Section II.B.3.b) (Al-Baradie *et al*., 2002; Michielse *et al*., 2006). [Note that diffuse granule cell hypoplasia may, in fact be better classified as congenital disorder of glycosylation (CDG) type 1a (IV.B), as suggested by Pascual-Castroviejo *et al*. (2006). It is temporarily included in both categories.] The *Ptf1a* gene encodes a basic helix-loop-helix transcription factor that has been shown to be expressed in progenitor cells in the ventricular zone of the dorsal aspect or rhombomere 1; the protein product is required for the generation of GABAergic cells (Purkinje cells and interneurons) in the cerebellum (Hoshino *et al*., 2005), neurons of the inferior olivary nuclei (Yamada *et al*., 2007), and specification of dorsal interneurons in the spinal cord (Glasgow *et al*., 2005). [It is also necessary for the specification and formation of the pancreas (Hoshino *et al*., 2005).] The number of granule cells generated is extremely reduced when Purkinje cells are not located in their normal position and in normal numbers (Wetts and Herrup, 1982; Sotelo, 2004). In animal models, Purkinje cells regulate proliferation of granule cell precursors via secretion of Shh, perhaps by upregulation of *Nmyc* (Wallace, 1999; Kenney *et al*., 2003; Hoshino, 2006). Granule cells are reduced in number by any process that reduces the number of viable Purkinje cells. Thus, just as accentuated apoptosis can cause cerebral hypoplasia, it causes cerebellar hypoplasia, as well (Kaindl *et al*., 2006; Takano *et al*., 2006). In humans, mutations of *PTF1A* result in profound cerebellar hypoplasia (Fig. 5) (Sellick *et al*., 2004; Hoshino *et al*., 2005). It will probably take time for all of the precise causes of cerebellar hypoplasia to become fully elucidated; as these causes become better understood, this classification can be appropriately modified.

Several reports have described seven patients in whom the superior portion of the brain stem is connected to the inferior portion of the brain stem by a thin cord of tissue (Mamourian and Miller, 1994; Sarnat *et al*., 2002; Bednarek *et al*., 2005; McCann *et al*., 2005; Poretti *et al*., 2007*b*; Barth *et al*., 2008); these have been referred to as brain stem 'disconnection syndromes'. In three of the patients, the disconnection was in the lower midbrain/upper pons (I.A.2.b) and in four it was in the lower pons/upper medulla (I.A.3.b, Fig. 6). Neuropathological analysis of two cases by Sarnat *et al*. (2002) showed a thin midline cord passing from the upper segment to the lower segment with hypoplasia of the cerebellar vermis and hemispheres and an anomalous basilar artery. Histological investigation revealed a poorly organized mixture of neurons in the tegmentum, but no evidence of any gliotic lesions to suggest hypoxia or ischaemia; this was interpreted as providing evidence in favour of a brain stem malformation, rather than a disruption (Sarnat *et al*., 2002). In contrast, Barth *et al*. (2008) found central cavitation that they interpreted as more of a syrinx and postulated a vascular cause. It is, indeed, possible that some 'disconnection' syndromes might be described as examples of segmental dysgenesis in which segments of the midbrain and hindbrain do not develop normally, perhaps as a result of malexpression of the genes that are responsible for segmentation. One of the authors has seen a case of disconnection syndrome associated with periventricular nodular heterotopia, a finding that supports a genetic aetiology. In avian and murine models, the formation of the rhombomeres is closely related to expression of *Hox* genes, a set of chromosomally clustered genes whose close relatives are known to specify positional values along the main body axis of the fly embryo (Lumsden, 2004). In avian models, the loss of *Hoxa1* function, for example, results in deletion of rhombomere 5, reduction of rhombomere 4, and loss of specific neuronal nuclei (I.A.3.c.) (Mark *et al*., 1993). Another possibility is that disruption of the upstream modulators of *Hox* genes, such as *Krox20* and *Mafb*, may be responsible for these disconnections (Lumsden, 2004). However, in animal models, deletion of a rhombomere results in a shortened brain stem, but not in a 'gap' within the brain stem (Lumsden, 2004). In addition, it is important to remember that early vascular

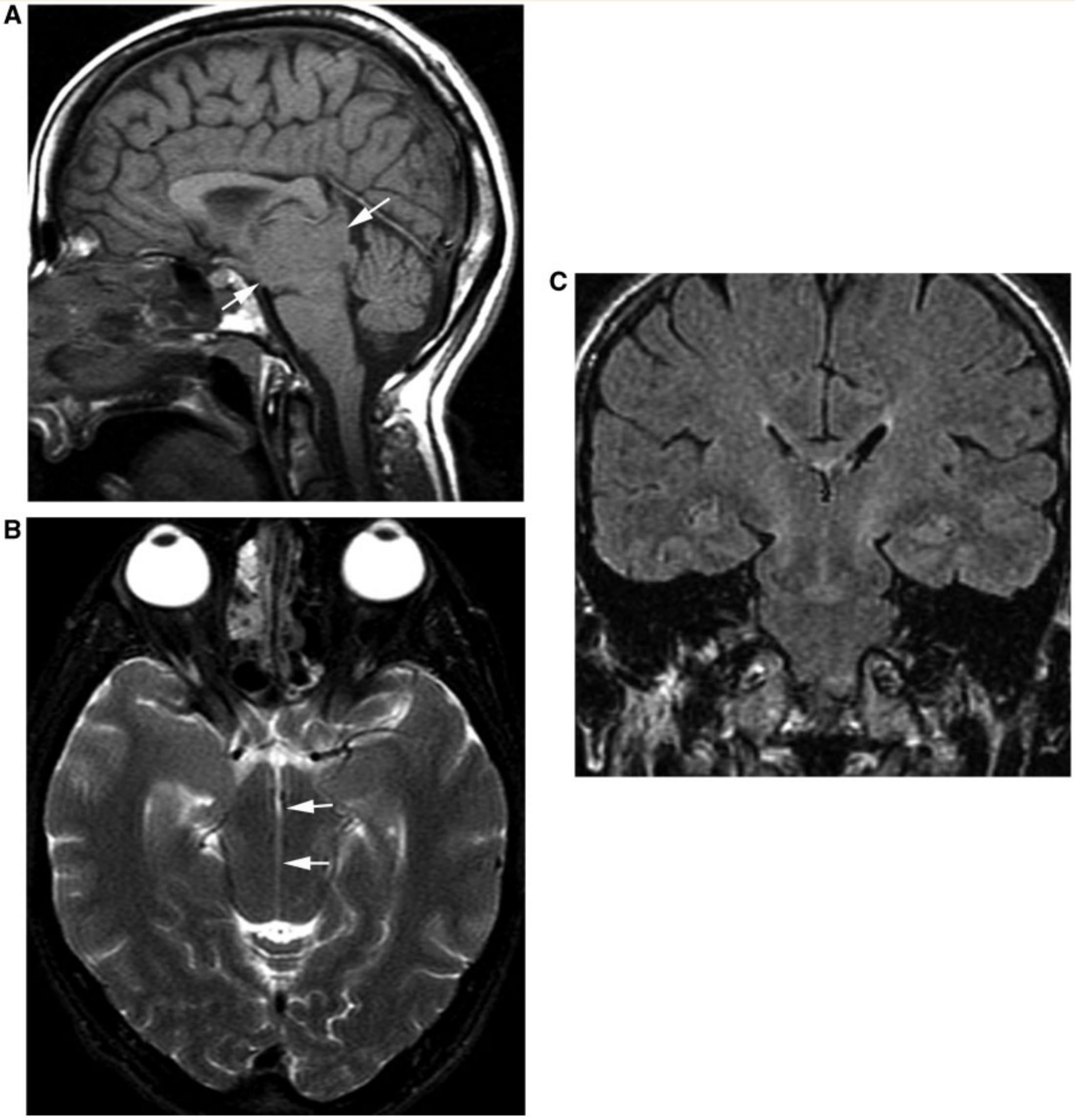

Figure 4 Abnormality of diencephalic-mesencephalic junction. (**A**) Sagittal T_1-weighted image shows a thick midbrain (arrows) and a poorly-defined junction between the midbrain and the diencephalon. (**B**) Axial T_2-weighted image shows that the hypothalamus and midbrain appear to merge, and the third ventricle (arrows) seems to extend into the midbrain. C. Coronal fluid attenuation inversion recovery image shows the midbrain seemingly continuous with the thalami.

disruptions in the brain result in tissue liquefaction without glial response. Thus, gliosis would not be expected from an early segmental injury, and so an early vascular or toxic injury to the brain stem might be more likely. Further work with animal models or identification of families with these malformations may help to further elucidate these mechanisms.

In mouse models, absence of several cranial nerves has resulted from abnormal expression of anteroposterior patterning genes (I.A.3.c), including *Wnt1* (trigeminal nerve), *Gbx2* (trigeminal nerve), *Hoxb1* (loss of facial motoneurons, absent facial nerve), *Hoxb2* (absent facial nerve), and *Hoxa3* (hypoplasia of IXth cranial ganglia) (Cordes, 2001; ten Donkelaar *et al*., 2006). In *Krox20*$^{-/-}$ mice, rhombomeres 3 and 5 do not develop, the abducens nucleus and the visceromotor component of the facial nerve are absent, and the axons of trigeminal motoneurons join the facial nerve and enter the second pharyngeal arch (Schneider-Maunoury *et al*., 1997). These axons do not find the muscles of mastication (their proper targets), so the parent motoneurons undergo apoptosis (Schneider-Maunoury *et al*., 1997). It is likely that some mutations of the corresponding human genes will eventually be found in patients with congenital cranial neuropathies.

Segmental shifts in the brain stem are also present in humans with Athabaskan brainstem dysgenesis syndrome (seen in Native American tribes) and Bosley-Salih-Alorainy syndrome (observed in Saudi and Turkish families), both caused by homozygosity for mutations of *Hoxa1* (Bosley *et al*., 2008), resulting in horizontal gaze abnormalities, hearing loss, facial weakness, hypoventilation, mental retardation and autism spectrum disorder (Tischfield *et al*., 2005). Anomalies of the vascular system and the inner ear may be seen as well (Tischfield *et al*., 2005).

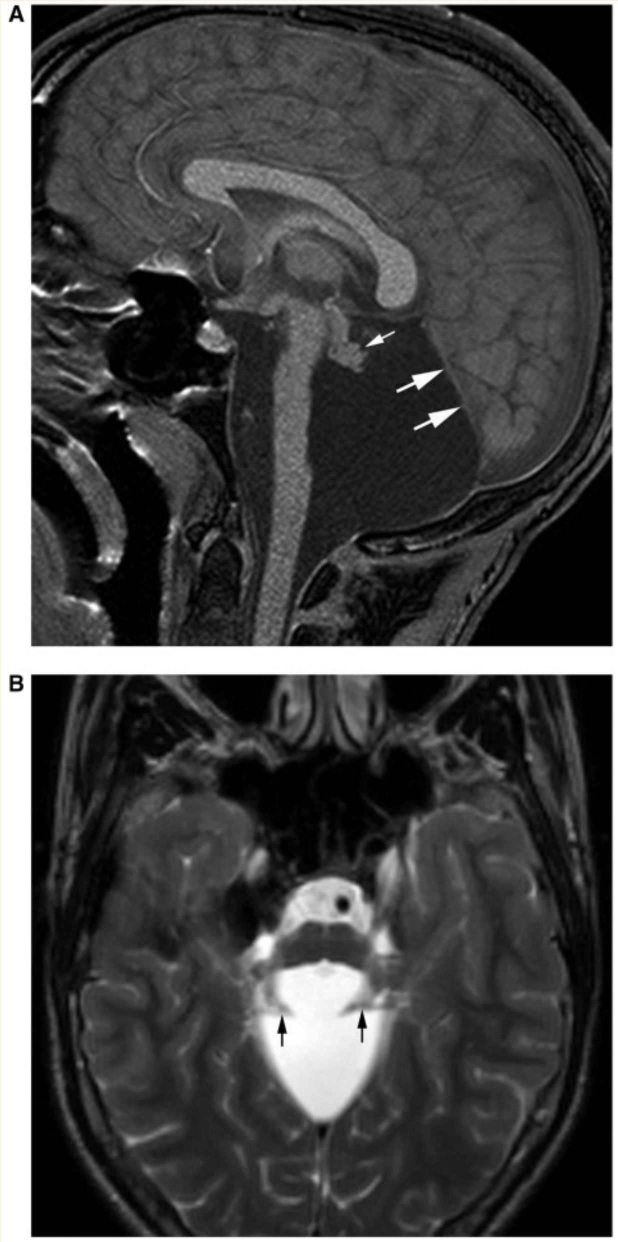

Figure 5 Profound cerebellar hypoplasia due to *PTF1A* mutation. (**A**) Sagittal T_1-weighted image shows an extremely small cerebellar vermis (small arrow) and small posterior fossa with low tentorium (arrows) and occipital lobes. (**B**) Axial T_2-weighted image shows extremely small cerebellar hemispheres (arrows).

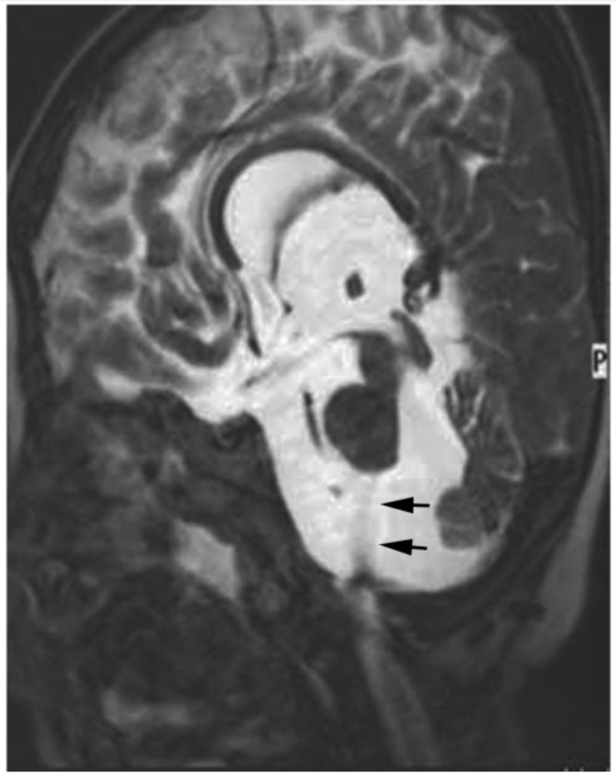

Figure 6 Hindbrain disconnection syndrome. Sagittal T_2-weighted image shows nearly complete absence of the medulla, with only a few fibres (arrows) appearing to connect the somewhat small pons to the spinal cord. Controversy exists concerning the cause (genetic or acquired) of this syndrome.

Group II. Generalized brain malformations that significantly affect the brain stem and cerebellum

Malformations in Group II are best classified as generalized brain disorders but involvement of the midbrain and hindbrain is so significant that they need to be included in this classification. Some of these disorders affect cell proliferation, others are believed to primarily affect cell migration, while still others are associated with defects in ciliary proteins and, therefore, probably affect cell migration, axon navigation, and possibly other aspects of brain development.

The first group in this section (Group II.A, Table 3) is mid-hindbrain malformations in association with developmental encephalopathies, a term used to describe mental retardation, autism-spectrum disorders, Rett syndrome, and other similar disorders. For example, a number of families with mental retardation or autism and nonprogressive cerebellar hypoplasia (Illarioshkin *et al*., 1996; Illarioshkin *et al*., 1999; Gardner *et al*., 2001; Tsao *et al*., 2006; Ventura *et al*., 2006) or isolated vermian hypoplasia (Courchesne *et al*., 1988; Carper and Courchesne, 2000; Bergmann *et al*., 2003; Philip *et al*., 2003; van Amelsvoort *et al*., 2004; Zinkstok and van Amelsvoort, 2005; Bish *et al*., 2006; Boland *et al*., 2007; Hill *et al*., 2007; Poot *et al*., 2007; van Bon *et al*., 2008; Webb *et al*., 2009) have been described, including some with mutations of oligophrenin 1 (*OPHN1*) (Zanni *et al*., 2005) and one found to have a locus in Xp11.21-q24 (Illarioshkin *et al*., 1999).

An important, and only recently described, group is mesenchymal-neuroepithelial signalling defects (Group II.B, Table 4). Work in Forkhead box C1 (*Foxc1*) knock-out mice has shown that, even though the gene is expressed only in the posterior fossa mesenchyme overlying the cerebellum, absence of Foxc1 deficiency results in cerebellar hypoplasia (Aldinger *et al*., 2009). In humans, mutations of *FOXC1* cause a range of posterior fossa

Table 3 **Group II.A. Developmental encephalopathies associated with mid-hindbrain malformations (these include mental retardation, autism spectrum disorders, schizophrenia, Rett-like disorders and others)**

Defects	Examples	Comments and references
II.A.1. Developmental encephalopathies associated with diffuse cerebellar hypoplasia	Mouse mutants • Grid2$^{-/-}$ (lurcher mouse) • Rora$^{-/-}$ (staggerer mouse) • Girk2$^{-/-}$ (weaver mouse) Human by phenotype • Isolated cerebellum agenesis • X–linked non-progressive cerebellar hypoplasia » XL locus in Xp11.21-q24 • Mental retardation, epilepsy with cerebellar hypoplasia • AD (or XL) cerebellar hypoplasia with improvement	This is most likely a heterogeneous group that needs further attention. (Illarioshkin *et al*., 1996, 1999; Gardner *et al*., 2001; Chizhikov and Millen 2003; Tsao *et al*., 2006; Ventura *et al*., 2006; Gold *et al*., 2007; Vogel *et al*., 2007)
II.A.2. Developmental encephalopathies associated with cerebellum vermis hypoplasia	Human by phenotype • Mental retardation with cerebellar vermis hypoplasia » OPHN1$^{-/Y}$ » del 1q44, del 22q11.2 • Autism with cerebellum vermis hypoplasia	The link between autism and developmental defects of the cerebellum is now reasonably well established after years of controversy. The basis for the link is not understood. The oligophrenin 1 protein participates in morphogenesis and function of dendritic spines. (Courchesne *et al*., 1988; Carper and Courchesne 2000; Bergmann *et al*., 2003; Philip *et al*., 2003; van Amelsvoort *et al*., 2004; Zanni *et al*., 2005; Zinkstok and van Amelsvoort 2005; Bish *et al*., 2006; Boland *et al*., 2007; Hill *et al*., 2007; Poot *et al*., 2007; van Bon *et al*., 2008; Webb *et al*., 2009)
II.A.3. Developmental encephalopathies associated with BS (especially pontine) hypoplasia	Mouse mutants • Nscl1/2$^{-/-}$ with pontine hypoplasia Human by phenotype • Pontine hypoplasia	(Barkovich *et al*., 2007; Schmid *et al*., 2007)

Only limited data regarding pathogenesis are available for most disorders placed here. Some are probably due to defects in cell fate (downstream signalling) or cell maintenance.

Table 4 **Group II.B. Mesenchymal-neurepithelial signalling defects associated with mid-hindbrain malformations**

Defects	Examples	Comments and references
II.B.1.Combined cerebellar and posterior fossa malformations	Mouse mutants • Zic1$^{+/-}$;Zic4$^{+/-}$ • Foxc1$^{-/-}$ Human by phenotype • Cerebellum vermis hypoplasia • Mega-cisterna magna with cerebellum vermis hypoplasia • Dandy-Walker malformation » *Foxc1*$^{+/-}$ » del 3q24 (loss of *ZIC1-ZIC4*), del 6p25.3 (loss of *FOXC1*), dup 9p, del 13q2, dup 17p13.3 » AD locus 2q36.1 • Neurocutaneous melanosis • PHACES syndrome with Dandy–Walker malformation	Our data demonstrate a spectrum of cerebellar malformations including classic Dandy–Walker malformation in humans with mutations of FOXC1, which signals from mesenchyme to cerebellum, but is not expressed in the cerebellum itself (Aldinger *et al*., 2009). [Narayanan *et al*., 1987; Kadonaga *et al*., 1992; Melaragno *et al*., 1992; Barkovich *et al*., 1994; Frieden *et al*., 1996; McCormack *et al*., 2002, 2003; Cazorla Calleja *et al*., 2003; Bhattacharya *et al*., 2004; Grinberg *et al*., 2004; Acosta Jr *et al*., 2005; Chen *et al*., 2005; Ballarati *et al*., 2007; Jalali *et al*., 2008; Aldinger *et al*., 2009 (in revision)]
II.B.2. Posterior fossa anomalies largely sparing the cerebellum	Human by phenotype • Arachnoid cysts of posterior fossa • Mega-cisterna magna, isolated	Mega-cisterna magna in this group consists of an enlarged posterior fossa with normal size of cerebellum (Barkovich *et al*., 1989; Siebert 2006)

The rationale for this group comes from our data showing that loss of mesenchymal expression of FOXC1 leads to combined cerebellar and posterior fossa malformations (Aldinger *et al*., 2009).

anomalies ranging from vermis predominant cerebellar hypoplasia to mega cisterna magna to Dandy–Walker malformation (Aldinger *et al*., 2009). Similar ranges of posterior fossa anomalies (Fig. 7) have been described with deletion of 3q24 (loss of *ZIC1-ZIC4*) (Grinberg and Millen, 2005), duplication of 9p (Melaragno *et al*., 1992; Cazorla Calleja *et al*., 2003; Chen *et al*., 2005), deletion of 13q2 (McCormack *et al*., 2003; Ballarati *et al*., 2007), and deletion of 2q36.1 (Jalali *et al*., 2008), as well as in neurocutaneous

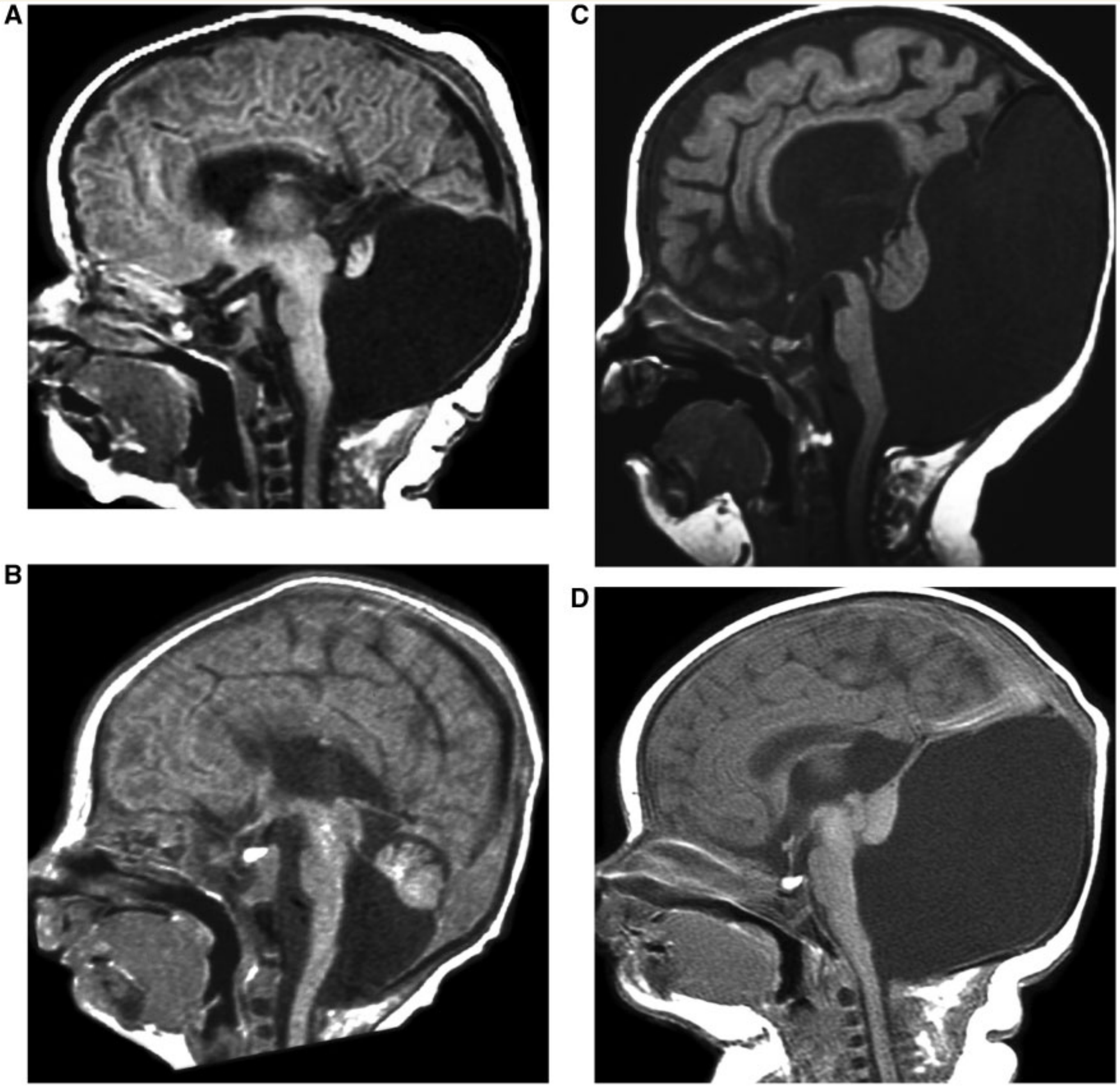

Figure 7 Dandy–Walker malformations with multiple associated genetic/clinical disorders. All show a small cerebellum and a CSF containing structure that expands the posterior fossa; these seem to result from mutations of genes that affect both leptomeningeal and cerebellar development. Similar appearances are seen in patients with different gene mutations, while different appearances are seen in patients with mutations of the same gene. (**A**, **B**) Patients with deletion 3q24; note the markedly different severity of the hindbrain malformation. (**C**) Patient with deletion 6p25.3. (**D**) Patient with PHACES syndrome.

melanosis (Kadonaga *et al*., 1992; Barkovich *et al*., 1994; Acosta Jr *et al*., 2005) and PHACES (Posterior fossa malformations, Haemangioma, Arterial anomalies, Cardiac abnormalities/aortic coartation, Eye abnormalities, Sternal cleft defects) syndrome (Frieden *et al*., 1996; Metry *et al*., 2001), raising the possibility of significant effects of the developing leptomeninges upon MB-HB development. The finding of malformations of the leptomeninges (arachnoid cysts, mega cisternae magnae, meningoceles), which are derived from cranial mesenchyme, in some of the same families suggests that these malformations belong within the same group (II.B.2).

A number of malformations are proposed to result from abnormal cell proliferation (Group II.C, Table 5); these include decreased proliferation, increased proliferation, and proliferation of dysplastic cells. Increased proliferation (Group II.C.2) is very uncommon; it is mainly seen in the macrocephaly-capillary malformation syndrome (Conway *et al*., 2007), which has many similarities to the megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome and is likely to be closely related to it (Gripp *et al*., 2009). Both have overgrowth of cerebral and cerebellar hemispheres that often result in cerebellar tonsillar herniation and sometimes Chiari 1 malformation. Proliferation of abnormal cells (Group II.C.1) predominantly results in focal areas of overgrowth containing dysplastic cells. Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease) and cerebellar cortical hamartomas (of tuberous sclerosis) are both mass-like disorders that are composed of dysplastic, rather than neoplastic, cells and are, therefore, included in this section. Lhermitte-Duclos is characterized pathologically by enlarged, circumscribed cerebellar folia containing large ganglion cells in the granular cell layer and prominent myelinated tracts in the outer molecular layer. However, the histology is variable, ranging from a recognizable granular cell layer containing occasional large dysplastic neuronal cell bodies, to an unrecognizable granular layer occupied by a population of large nerve cell bodies between the molecular layer and internal white matter (Ambler *et al*., 1969). The hypertrophic granule cells express neurofilament protein in a manner similar to Purkinje cells, and it has been postulated that the increased expression of neurofilament proteins by the cerebellar granule cells may account for their hypertrophy and subsequent axonal enlargement leading to myelination within the molecular layer of the cerebellar cortex (Yachnis *et al*., 1988). Nearly 50% of cases are associated with Cowden syndrome, an autosomal dominant syndrome caused by mutations of the *PTEN* gene at 10q23.31, and characterized by multiple hamartomas throughout the body (Marsh *et al*., 1999). Cortical tubers of tuberous sclerosis, caused by mutations of either the *TSC1* (at 9q34) or *TSC2* (at 16p13) gene are composed of a coarse subpial gliosis, abnormal cortical lamination with many large, abnormal, often multinucleated cells, and multiple heterotopic subcortical neurons (Norman *et al*., 1995); the finding of cerebellar tubers is common (Eluvathingal *et al*., 2006). The effect of these cerebellar lesions upon outcome is not understood. Hemimegalencephaly is a poorly understood malformation of cerebral cortical development, composed of dysmorphic cells (both neuronal and glial) that are often in abnormal locations (Robain and Gelot, 1996; Flores-Sarnat, 2002; Flores-Sarnat *et al*., 2003). This most often occurs as an isolated malformation, but may be associated with epidermal nevus (linear nevus sebaceous of Jadasohn) or other neurocutaneous syndromes (Peserico *et al*., 1988; Pavone *et al*., 1991; Pelayo *et al*., 1994; Griffiths *et al*., 1994), or with tuberous sclerosis (Griffiths *et al*., 1998; Galluzzi *et al*., 2002) or other phakomatoses (Cusmai *et al*., 1990; Dhamecha and Edwards-Brown, 2001). The reason for the presence of ipsilateral cerebellar hemispheric enlargement and dysplasia in some cases (Sener, 1997) is even more poorly understood.

Microcephalies with (disproportionately) decreased cerebellar cell proliferation (Group II.C.3) mostly have autosomal recessive inheritance (Albrecht *et al*., 1993; Sztriha *et al*., 1998; Hashimoto *et al*., 1998; Rajab *et al*., 2003) [although *CASK* mutations cause microcephaly with disproportionate cerebellar hypoplasia via X-linked inheritance (Najm *et al*., 2008)]. Many patients with developmental microcephaly (in contrast to those with acquired microcephaly) have cerebella that are proportionally small when compared to the cerebrum (Fig. 8) (Barkovich *et al*., 1998; Bellini *et al*., 2002; Kelley *et al*., 2002; Sheen *et al*., 2004; Chandler *et al*., 2006), suggesting that many of the same processes controlling cell proliferation or apoptosis apply in both the supra- and infratentorial compartments. Other patients with microcephaly (Hoveyda *et al*., 1999; Hoshino *et al*., 2005; Sztriha *et al*., 2005; Sztriha and Johansen, 2005) and some with normal head size (Patel and Barkovich, 2002) have disproportionately small cerebella, suggesting that developmental processes differ in the supra- and infratentorial compartments.

Many other malformations of cortical development are associated with MB-HB developmental abnormalities (Table 6), including lissencephalies (Group II.D.1), cerebral heterotopia (Group II.D.2), cerebral polymicrogyria (Group II.D.3), and cobblestone-like malformations with defects of the pial basement membrane (Group II.D.4). The association of cerebellar hypoplasia with cerebral heterotopia and polymicrogyria is not understood. The reason for cerebellar hypoplasia associated with lissencephaly (Ross *et al*., 2001), even when head size is normal, is not always known; as discussed in the previous section, some pathways and processes that are more involved in cerebellar than cerebral development are affected in these cases. Alternatively, the cerebellar hypoplasia may result from associated Purkinje cell involvement, or failure of connection of Purkinje cells with granule cells, causing subsequent apoptosis of the granule cells. In *DCX* and *LIS1* mutations, the cerebellar hypoplasia is inconsistent and, when present, is rather mild (Ross *et al*., 2001). It is more consistently seen in *DCX* mutations rather than in *LIS1* mutations (unpublished results), and is severe in a significant number of patients with *TUBA1A* mutations (Bahi-Buisson *et al*., 2008; Fallet-Bianco *et al*., 2008; Morris-Rosendahl *et al*., 2008). The mid-hindbrain is particularly severely affected in patients with *RELN* and *VLDLR* associated cortical malformations (Group II.D.1.b), in which the brain stem shows malpositioning of neurons (Nishikawa *et al*., 2003) and the cerebellum is extraordinarily small and smooth (nearly afoliar, Fig. 9) (Hong *et al*., 2000; Boycott *et al*., 2005). Reelin is a secreted glycoprotein that regulates neuronal positioning in cortical brain structures and the migration of neurons along the radial glial fibre network by binding to lipoprotein receptors VLDLR (very low density lipoprotein receptor) and APOER2 (apolipoprotein E receptor 2, or low density lipoprotein receptor-related protein 8) and the adapter protein disabled-1 (DAB1) (Hiesberger *et al*., 1999). In the cerebellum, Reelin regulates Purkinje cell alignment (Miyata *et al*., 1997) and granule cell proliferation (Wechsler-Reya and Scott, 1999), which are necessary for the formation of a normal sized cerebellum, as well as a well-defined cortical plate through which granule cells migrate to form the internal granular layer (Rakic and Sidman, 1970). Although both protein products function in the same pathway, *RELN* mutations seem to have a more severe effect than *VLDLR* mutations on

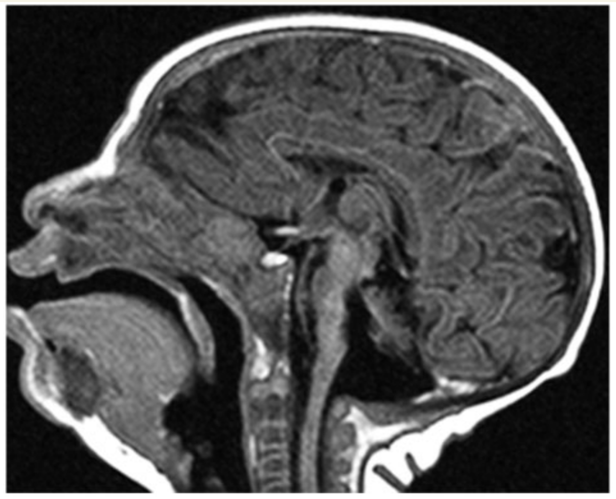
Figure 8 Microcephaly with disproportionate midbrain-hindbrain hypoplasia. Sagittal T_1-weighted image in a microcephalic neonate shows disproportionately small brainstem and cerebellum.

Table 5 Group II.C. Malformations of neuronal and glial proliferation that prominently affect the brainstem and cerebellum

Defects	Examples	Comments and references
II.C.1. Diffuse dysplasia with abnormal cell types, more severe in cerebellum	Mouse mutant • $Pten^{cko}/^{cko}$ Human by phenotype • Tuberous sclerosis » $TSC1^{+/-}$ » $TSC2^{+/-}$ • Cowden syndrome and Lhermitte-Duclos disease » $PTEN^{+/-}$ • Hemimegalencephaly with ipsilateral cerebellomegaly	The abnormalities here are focal areas of overgrowth and dysplasia. (Eng *et al*., 1994; Nelen *et al*., 1996; Sener 1997; Backman *et al*., 2001; Eluvathingal *et al*., 2006)
II.C.2. Megalencephaly associated with (probably) disproportionate cerebellomegaly and (in humans) cerebellar tonsilar herniation and Chiari 1 malformation	Human by phenotype • Macrocephaly-capillary malformation syndrome including MPPH (megalencephaly-polymicrogyria-polydactyly-hydrocephalus) • Costello syndrome » HRAS gain of function mutations	Macrocephaly-capillary malformation syndrome may be complicated by cerebellum tonsilar herniation and Chiari malformation (Conway *et al*., 2007). Our data suggest that macrocephaly-capillary malformation and MPPH syndromes represent either a single syndrome, or related disorders in the same pathway (Gripp *et al*., 2009). We have data on Costello syndrome showing cerebellum tonsilar herniation and Chiari similar to macrocephaly-capillary malformation.
II.C.3. Microcephaly with severe and disproportionate brainstem and cerebellar hypoplasia	Mouse mutants • $CASK^{-/Y}$ and $CASK^{+/-}$ (male and female) Human by phenotype • Severe congenital microcephaly with disproportionate Brainstem and cerebellum hypoplasia and variable enlarged extra-axial spaces • Postnatal microcephaly with disproportionate brainstem and cerebellar hypoplasia » $CASK^{+/-}$, $CASK^{-/Y}$ • Postnatal microcephaly and diffuse cerebellum hypoplasia with spasticity, autosomal recessive » Locus in 7q11–q21	While CASK is X-linked, most disorders in this group have autosomal recessive inheritance. One of these was described as a form of pontocerebellar hypoplasia (Rajab *et al*., 2003), but we interpret this as diffuse cerebellum hypoplasia. (Albrecht *et al*., 1993; Hashimoto *et al*., 1998; Sztriha *et al*., 1998; Rajab *et al*., 2003, 2007; Najm *et al*., 2008)

both the cerebral and cerebellar malformations. The reason for the difference is not known at this time, although it is probably related to the fact that reelin has multiple other receptors, including ApoER2, that result in different downstream effects and that these effects differ in the mid- and hindbrain compared to the forebrain (Gressens, 2006; Hack *et al*., 2007).

The so-called dystroglycanopathies (Group II.D.4), believed to be caused by impaired O-mannosylation of α-dystroglycan (Moore *et al*., 2002; Beltran-Valero de Bernabe *et al*., 2004; van Reeuwijk *et al*., 2005; Kanagawa and Toda, 2006; Saito *et al*., 2006; Martin, 2007), are associated with congenital muscular dystrophy and variable eye and brain anomalies. The brain abnormalities are sometimes called cobblestone malformation and involve the cerebrum, brain stem, and cerebellum. In these disorders, abnormal O-glycosylation of α-dystroglycan in the basal lamina of the pial basement membrane is postulated to result in abnormal fusion of the endfeet of radial glial cells with the basal lamina and gaps in the pial basement membrane; migrating neurons do not receive proper ‘stop’ signals and overmigrate into the subpial space (van Reeuwijk *et al*., 2005, 2006; Kanagawa and Toda, 2006; Saito *et al*., 2006; Martin, 2007). In the cerebellum, affected patients have variable degrees of dysmorphism, ranging from abnormal cortical foliation with a few cortical/subcortical cysts (Fig. 10) to profound cerebellar hypoplasia and dysmorphism with greater involvement of the vermis than the hemispheres (Fig. 11). The malformation may be related to disturbances in the external granule cell layer (Henion *et al*., 2003). The brain stem is affected in nearly all patients, manifesting enlarged quadrigeminal plates, fusion of the colliculi, and hypoplasia of the pons, often with a longitudinal ventral midline pontine cleft (Figs 10 and 11) (Barkovich *et al*., 2007). The small pons with midline cleft may be caused by hypoplasia of the middle cerebellar peduncles resulting in hypoplasia of their decussation; another component of the pontine hypoplasia may relate to impaired tangential migration of pontine nuclear neurons as shown in murine models of *Large* mutations (Qu *et al*., 2006). Thus, as in the cerebral hemispheres, the midbrain-hindbrain disorder appears to be the result of both abnormal neuronal migration and abnormal formation of white matter tracts. We know of several similar malformations associated with subtle differences in both the glycosylation defects and the clinical phenotype (Group II.D.4.b), including those due to mutations of *GPR56* [often called bilateral frontoparietal polymicrogyria (Chang *et al*., 2003)], *ATP6V0A2* [associated with Debré type cutis laxa (Kornak *et al*., 2008; Van Maldergem *et al*., 2008)], and *SNAP29* [which is associated with cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma (CEDNIK) syndrome (Sprecher *et al*., 2005)]. Recent work shows that G protein-coupled receptor (GPR) 56 has a role in the organization of the pial basement membrane and in the regulation of anchorage of radial glial endfeet (Li *et al*., 2008).

Table 6 Group II.D. Malformation of neuronal migration that prominently affect the brainstem and cerebellum

Defects	Examples	Comments and references
II.D.1. Lissencephaly with cerebellar hypoplasia (LCH)		
II.D.1.a Lissencephaly with cerebellar hypoplasia (LCH), new mutation autosomal dominant and X-linked inheritance	Mouse mutants • Lis1$^{+/-}$ and Lis1$^{+/cko}$ • Tuba1a$^{+/-}$ (heterozygous partial loss of function) • Dcx$^{-/Y}$ (obvious in rat, subtle in mouse) » Each of these mutants has deficient neuronal migration in cerebrum and cerebellum. Human by genotype • DCX$^{-/Y}$, DCX$^{+/-}$ (males and females) » LCH in males corresponding to Ross LCH group a, and subcortical band heterotopia in females. Most have subtle cerebellum hypoplasia; a few have mild or moderate cerebellum hypoplasia. • LIS1$^{+/-}$ » LCH in males corresponding to Ross LCH group a. Most have subtle cerebellum hypoplasia; a few have mild or moderate cerebellum hypoplasia. • LIS1$^{+/-}$; YWHAE$^{+/-}$ » Miller-Dieker syndrome; most have subtle cerebellum hypoplasia; a few have mild or moderate cerebellum hypoplasia. • TUBA1A$^{+/-}$ » Most patients have Ross LCH group c with severe cerebellar and callosal hypoplasia, or group d with cerebellar hypoplasia only. Others have mild cerebellum hypoplasia (LCH group a), or lissencephaly with normal cerebellum by imaging.	A diagnosis of isolated lissencephaly sequence is used instead of LCH when the cerebellum appears normal on brain imaging studies, and is most common with DCX and LIS1 mutations. The LCH group includes classic or 4-layered lissencephaly in LCH group a, subcortical band heterotopia, and probably 2-layered lissencephaly in LCH groups c (which includes our prior group f) and d (see text and Ross *et al*., 2001). (Hirotsune *et al*., 1998; Ross *et al*., 2001; Cardoso *et al*., 2003; Toyo-oka *et al*., 2003; Forman *et al*., 2005; Keays *et al*., 2007; Morris-Rosendahl *et al*., 2008;)
II.D.1.b. LCH with hippocampal hypoplasia and nearly afoliar cerebellum, autosomal recessive inheritance	Mouse mutants • Reln$^{-/-}$ (reeler mouse) • Dab1$^{-/-}$ (scrambler and yotari mice) • Vldlr$^{-/-}$; Lrp8$^{-/-}$ Human by genotype • RELN$^{-/-}$ • VLDLR$^{-/-}$ » Ross LCH group b with mild frontal lissencephaly, small dysplastic hippocampus and severe afoliar cerebellum hypoplasia; the RELN phenotype is more severe than the VLDLR phenotype	Mouse knockouts have inverted cortex, while humans have moderate frontal predominant lissencephaly in addition to severe cerebellum hypoplasia. (Trommsdorff *et al*., 1999; Hong *et al*., 2000; Ross *et al*., 2001; Boycott *et al*., 2005; Chang *et al*., 2007; Zaki *et al*., 2007)
II.D.1.c. LCH, other types	Human by phenotype • Ross LCH groups c and d not associated with TUBA1A mutations • Ross LCH group e	LCH group e consists of lissencephaly with sudden transition to simplified gyral pattern. (Ross *et al*., 2001; Forman *et al*., 2005)
II.D.2. Neuronal heterotopia with prominent brainstem and cerebellum hypoplasia		
II.D.2.a. Periventricular nodular heterotopia with cerebellum hypoplasia	Mouse mutants; Flna$^{-/-}$ Human • Periventricular nodular heterotopia with cerebellum vermis hypoplasia » FLNA$^{+/-}$, rarely FLNA$^{-/Y}$	HET may be diffuse or regional, and are sometimes asymmetric. (Moro *et al*., 2002; Parrini *et al*., 2006)
II.D.2.b. Periventricular nodular heterotopia with overlying polymicrogyria and prominent brainstem and cerebellum hypoplasia	Mouse » Map3k4$^{-/-}$ Human • Frontal-perisylvian Periventricular nodular heterotopia-polymicrogyria with cerebellum hypoplasia • Posterior Periventricular nodular heterotopia–polymicrogyria with cerebellum hypoplasia	(Wieck *et al*., 2005; Sarkisian *et al*., 2006)
II.D.2.c.. Subcortical nodular heterotopia with cerebellum hypoplasia	Human • Subcortical nodular heterotopia with dysplastic cortex, ACC, cerebellum hypoplasia	(Dubeau *et al*., 1995; Barkovich 2000)

(continued)

Table 6 Continued

Defects	Examples	Comments and references
II.D.3. Polymicrogyria with cerebellum hypoplasia	Mouse • *Tbr2*$^{-/-}$ Human • ACC-polymicrogyria-cerebellum hypoplasia » TBR2 • Aicardi syndrome • Delleman syndrome (Oculocutaneouscerebral syndrome)	(Aicardi *et al*., 1965; Ferrer *et al*., 1986; Aicardi 2005; Baala *et al*., 2007*a*)
II.D.4. Malformations with basement membrane and neuronal migration deficits		Most of the cobblestone and cobblestone-like (due to lack of pathological confirmation) brain malformations are associated with defects in glycosylation.
II.D.4.a. Cobblestone malformations with abnormal alpha-dystroglycan glycosylation	Mouse mutants • Dag$^{cko/cko}$ (conditional knockout in brain) • Large$^{-/-}$ » Both mutants have pial basement membrane disruption and other malformations similar to the human syndromes. Human by genotype • POMGnT1$^{-/-}$ » Muscle-eye-brain disease (MEB) and congenital muscular dystrophy (CMD) without recognized brain malformations • FCMD$^{-/-}$ » Walker-Warburg syndrome (WWS), Fukuyama congenital muscular dystrophy (FCMD) and congenital muscular dystrophy without brain malformations • FKRP$^{-/-}$ • LARGE$^{-/-}$ • POMT1$^{-/-}$ • POMT2$^{-/-}$ » Walker-Warburg syndrome, muscle-eye-brain disease and congenital muscular dystrophy without brain malformations	From most to least severe, the spectrum of cobblestone malformations-associated phenotypes includes Walker-Warburg syndrome, muscle-eye-brain disease, Fukuyama congenital muscular dystrophy and congenital muscular dystrophy without recognized brain malformations. All but POMGnT1 are associated with a wide spectrum of severity. (Kobayashi *et al*., 1998; Yoshida *et al*., 2001; Beltran-Valero de Bernabe *et al*., 2002, 2003, 2004; Holzfeind *et al*., 2002; Moore *et al*., 2002; Longman *et al*., 2003; Akasaka-Manya *et al*., 2004; Godfrey *et al*., 2007; Manzini *et al*., 2008)
II.D.4.b. Cobblestone-like malformations with variable glycosylation defects	Mouse mutants • Gpr56$^{-/-}$ Human by genotype • GPR56$^{-/-}$ » Bilateral fronto-parietal cobblestone-like malformation • ATP6V0A2$^{-/-}$ » CDG type 2 with Debré type cutis laxa with cerebellum vermis hypoplasia or Dandy–Walker malformation • B4GALT1$^{-/-}$ » CDG type 2d with cerebellum vermis hypoplasia or Dandy–Walker malformation • SNAP29$^{-/-}$ » CEDNIK syndrome	Brain imaging studies closely resemble those of classic muscle-eye-brain disease in all of these disorders, which thus differ from polymicrogyria. Two of them are classified as 'congenital disorders of glycosylation' (CDG). The Gpr56 knockout has pial basement membrane disruption. (Hansske *et al*., 2002; Peters *et al*., 2002; Piao *et al*., 2004, 2005; Morava *et al*., 2005; Sprecher *et al*., 2005; Kornak *et al*., 2008; Li *et al*., 2008; Van Maldergem *et al*., 2008; Koirala *et al*., 2009)

The most common forms of lissencephaly have mild cerebellum dysplasia easily seen by pathology but not by imaging.

GPR56 mutations affect cerebral cortical development by causing breaches in the pial basement membrane, thus allowing overmigration of neurons into the subpial space and resulting in a cobblestone-like malformation (Li *et al*., 2008). In the cerebellum, mouse models demonstrate that granule cells show loss of adhesion to extracellular matrix molecules of the pial basement membrane (Koirala *et al*., 2009). Both of these mechanisms are similar to what is seen in the dystroglycanopathies.

Group II.E consists of disorders known as Joubert syndrome and related disorders [JSRD; see Table 7 (Joubert *et al*., 1969; Boltshauser and Isler, 1977; Gleeson *et al*., 2004; Zaki *et al*., 2007), also called molar tooth malformations (Quisling *et al*., 1999)]. These disorders have abnormalities of white matter tracts in the brain stem and abnormal superior cerebellar peduncles (Fig. 12) as well as dysplasia of the cerebellar vermis and, often, accompanying abnormalities of the eyes (retinal dysplasia or colobomas), kidneys (nephronophthisis), limbs (preaxial, mesaxial, or postaxial polydactyly), liver (fibrosis), orofacial deformities, and other central nervous system anomalies (including occipital encephaloceles and cerebral polymicrogyria)

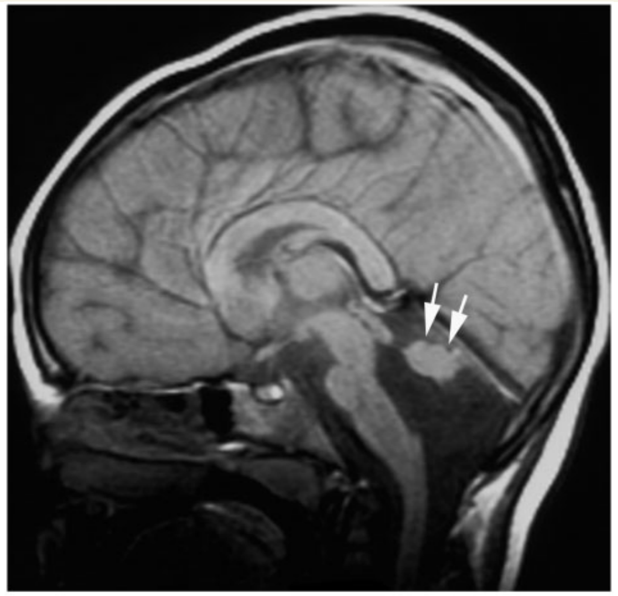

Figure 9 Cerebellar and pontine hypoplasia secondary to *VLDLR* mutation. Sagittal T_1-weighted image shows cerebral pachygyria and a very small, smooth cerebellum (arrows), characteristic of mutations involving the RELN pathway. The pons is always small with developmental cerebellar hypoplasia.

(Zaki *et al*., 2007). Zaki *et al*. (2008) have suggested a classification of these disorders based upon the associated anomalies, which we have adopted. JSRD seem to be caused by mutations of genes encoding ciliary and centrosomal proteins (Keeler *et al*., 2003; Valente *et al*., 2003; 2006*a, b*; Gleeson *et al*., 2004; Parisi *et al*., 2004; Louie and Gleeson, 2005; Badano *et al*., 2006; Sayer *et al*., 2006; Brancati *et al*., 2007; 2008; 2009; Baala *et al*., 2007*b*; Delous *et al*., 2007; Frank *et al*., 2008; Gorden *et al*., 2008). A consistent overlap between JSRD and Meckel-Gruber syndrome—an autosomal recessive and genetically heterogeneous lethal disorder characterized by a combination of renal cysts and other variable features including developmental anomalies of the central nervous system (typically occipital encephalocele), hepatic ductal dysplasia and cysts, and polydactyly (Baala *et al*., 2007*b*; Delous *et al*., 2007; Frank *et al*., 2008)—has been recognized, which is supported by discovery of mutations in several of the same genes. Thus, the two disorders represent different points along a single spectrum of malformations (Baala *et al*., 2007*b*; Delous *et al*., 2007; Frank *et al*., 2008). Although the precise mechanisms by which these mutations affect brain development are only starting to be elucidated (Arts *et al*., 2007; Chizhikov *et al*., 2007; Delous *et al*., 2007; Frank *et al*., 2008), it has been postulated that ciliary and centrosomal proteins may interact to respond to extracellular signalling or modulatory cues in renal and retinal homeostasis and in neuronal development (Louie and Gleeson, 2005; Badano *et al*., 2006; Valente *et al*., 2006*b*). Alteration of centrosomal dynamics can alter neuronal migration (Sapir *et al*., 2008), which may explain the severe vermian hypoplasia seen in affected patients (Quisling *et al*., 1999; Yachnis and Rorke, 1999). As growth cones of migrating neurons and pathfinding axons are similar, defective ciliary and centrosomal function could explain the aberrant axonal pathways in the midbrain and hindbrain in affected patients (Yachnis and Rorke, 1999; Widjaja *et al*., 2006; Poretti *et al*., 2007*a*).

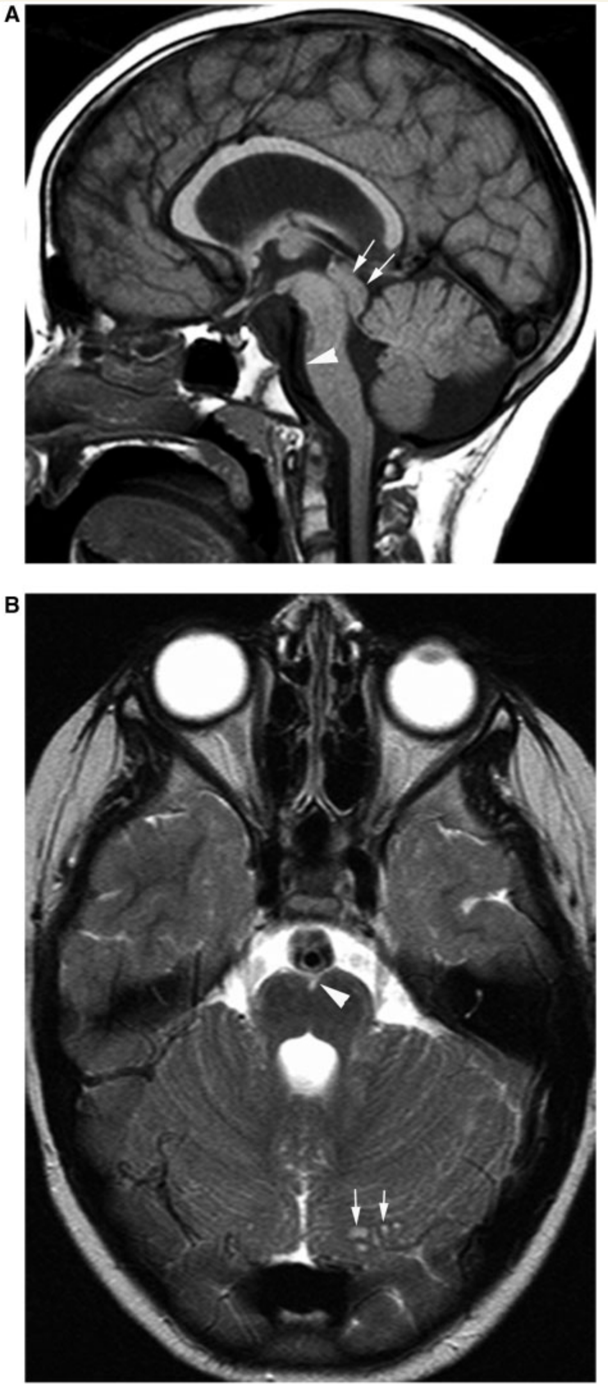

Figure 10 Midbrain and hindbrain malformations in mild dystroglycanopathy (muscle-eye-brain phenotype) due to *POMT1* mutation. (**A**) Sagittal T_1-weighted image shows abnormal vermian foliation, large, abnormally rounded quadrigeminal plate (small arrows) and flattened ventral pons (large arrowhead). (**B**) Axial T_2-weighted image shows ventral pontine cleft (arrowhead) and small cerebellar hemispheric cortical cysts (small arrows).

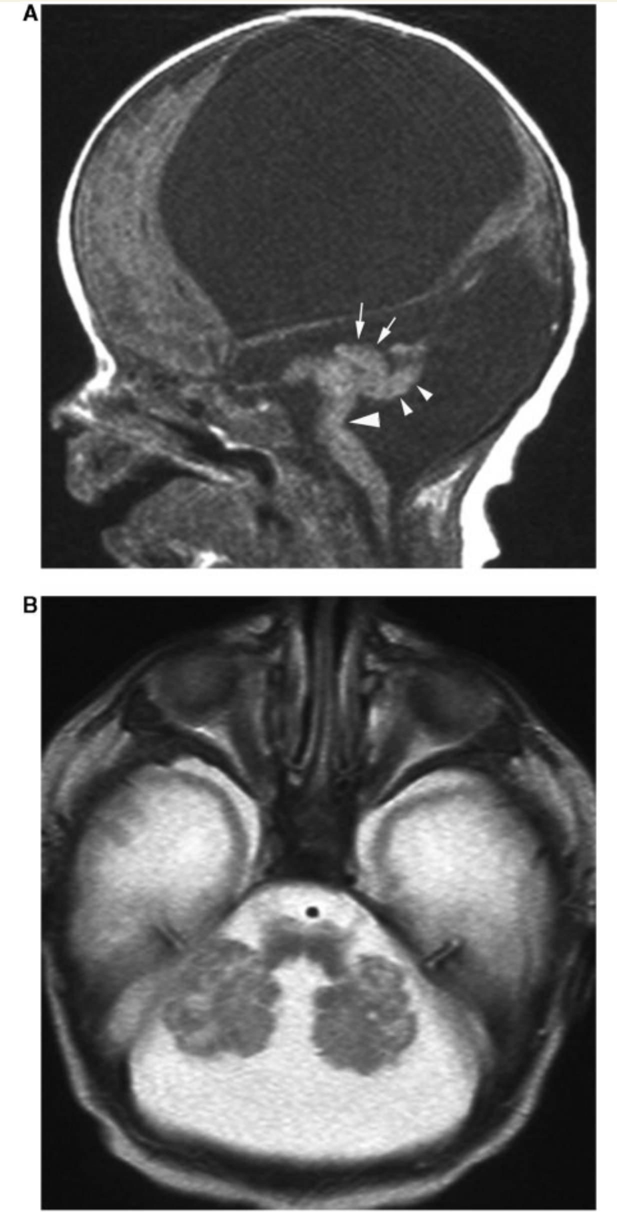

Figure 11 Midbrain and hindbrain malformations in severe dystroglycanopathy (Walker-Warburg phenotype). (**A**). Sagittal T_1-weighted image shows massive hydrocephalus, a very small, dysplastic vermis (small arrowheads), large, round tectum (small arrows) and small, ventrally kinked pons (large arrowhead). (**B**) Axial T_2-weighted image shows the extremely small, dysmorphic cerebellar hemispheres and the small pons with ventral midline cleft.

Group III. Regional developmental defects (localized brain malformations that significantly affect the brainstem and cerebellum, pathogenesis partly or largely understood)

Patients in this group (Table 8) have malformations of the brain stem or cerebellum that are localized and manifest clinically with neurological signs that are attributable to one anatomofunctional system rather than diffuse. Most are present from the time of birth, although some may not become evident until childhood.

Developmental clefts are included in this group. These may be seen in the dorsal or ventral midline surface of the pons, particularly in patients with cerebellar hypoplasia or dysplasia, but also in patients with normal cerebella (Barkovich *et al*., 2007). These are believed to result from impaired pathfinding of axons in the developing brain stem. The most common clefts are ventral longitudinal and midline, involving the pons. These are likely to be due to absence of the decussation of the middle cerebellar peduncles and possibly the transverse pontine axons migrating from the cerebellar cortex to the pontine nuclei. They are often associated with cerebellar hypoplasia, although they are also reported as a manifestation of generalized axonal midline crossing defects; when the midline-crossing defect is more generalized, the corpus callosum is often abnormal (Barkovich *et al*., 2007). Midline dorsal clefts are thought to result from abnormal development of the median longitudinal fasciculus and the tectospinal tract (Barkovich *et al*., 2007). The best studied of these is the condition known as horizontal gaze palsy with progressive scoliosis (Group III.A) (Thomsen *et al*., 1996; Trabousli, 2004; Bosley *et al*., 2005), a condition caused by mutations of the *ROBO3* gene, which codes for a netrin receptor that is required for midline crossing of hindbrain axons (Jen *et al*., 2004). Affected patients have congenital horizontal gaze palsy and MRI shows quite characteristic brain-stem hypoplasia with absence of the facial colliculi, presence of a deep midline dorsal pontine cleft (split pons sign), and a 'butterfly' configuration of the medulla (Fig. 13) (Rossi *et al*., 2004). Diffusion tensor tractography shows more extensive white matter abnormalities including absence of major pontine crossing axons and absence of decussation of the superior cerebellar peduncles in addition to reduced volume of dorsal longitudinal tracts in the pontine tegmentum (Sicotte *et al*., 2006), the latter being consistent with reduced volume or absence of the medial lemniscus and median longitudinal fasciculus. A dorsal longitudinal cleft in the midbrain (Group III.B) has been seen by one of the authors in a patient with trisomy 14 (AJB, unpublished observation). Several other brain stem disorders purportedly secondary to abnormal axonal pathfinding have been described (Barkovich *et al*., 2007). These include the recently reported pontine tegmental cap dysplasia, a malformation in which the ventral pons is hypoplastic due to absence of normal ventral decussation of the middle cerebellar peduncles while a band of horizontally oriented axons is present, instead, along the dorsal surface of the pons (Fig. 14) (Barth *et al*., 2007*b*; Jissendi-Tchofo *et al*., 2009). Other disorders that are presumably due the white matter guidance disruptions in the brain stem have been described recently (Barkovich *et al*., 2007) and the authors continue to find more, as yet unpublished, brain stem malformations. It is likely that an increasing number will be discovered as the quality of brain imaging improves, with higher field strength magnetic resonance scanners and as diffusion tensor tractographic methods become more robust.

Also included in this group are disorders caused by localized abnormalities of cell specification, such as the Duane retraction

Table 7 **Group II.E. Diffuse molar tooth type dysplasias associated with defects in ciliary proteins**

Defects	Examples	Comments and references
II.E.1. Syndromes affecting the brain with low frequency involvement of the retina and kidney	Human by genotype • JBTS1 locus chr9 • AHI1$^{-/-}$ (JBTS3 locus) • ARL13B$^{-/-}$ (JBTS8 locus) • CC2D2A$^{-/-}$ (JBTS9 locus) » Mutations of these genes cause classic Joubert syndrome with the typical JSRD neurological phenotype, molar tooth malformation, and occasional retinal and renal disease	(Saar *et al*., 1999; Dixon-Salazar *et al*., 2004; Ferland *et al*., 2004; Gleeson *et al*., 2004; Cantagrel *et al*., 2008)
II.E.2. Syndromes affecting the brain, eyes, kidneys, liver and variable other systems	• NPHP1$^{-/-}$ (JBTS4 locus) » Mutations of this gene usually cause renal cystic disease only, but rarely may cause a mild cerebello-oculo-renal syndrome phenotype • JBTS2 locus chr11 • CEP290$^{-/-}$ (JBTS5 locus) • MKS1$^{-/-}$ (MKS1 locus) • TMEM67$^{-/-}$ (MKS3, JBTS6 locus) • RPGRIP1L$^{-/-}$ (JBTS7 locus) » Mutations of these genes cause a wide spectrum of disease including (i) Meckel-Gruber syndrome (Meckel syndrome); (ii) the cerebello-oculo-renal syndrome variant with the JSRD neurological phenotype, molar tooth malformation, and often retinal, renal and liver disease; (iii) the COACH syndrome; (iv) classic Joubert syndrome; and (v) less common disorders without neurological problems such as Leber amaurosis. Human by phenotype • Oro-facio-digital syndrome type 6 (Varadi)	(Keeler *et al*., 2003; Valente *et al*., 2003, 2006*a*, *b*; Gleeson *et al*., 2004; Parisi *et al*., 2004; Sayer *et al*., 2006; Baala *et al*., 2007*b*; Brancati *et al*., 2007, 2008, 2009; Delous *et al*., 2007; Frank *et al*., 2008; Gorden *et al*., 2008)

The syndromes in this group are collectively referred to as Joubert syndrome and related disorders (JSRD), and are associated with the striking molar tooth malformation of the midbrain and hindbrain. The neurological phenotype includes cognitive and behavior problems, congenital oculomotor apraxia, ataxia and alternating hyperpnea-apnea. All syndromes in this group have autosomal recessive inheritance, and all genes so far identified code for ciliary proteins.

syndrome [a congenital sixth cranial nerve paralysis caused by deletion of *CHN1* (Al-Baradie *et al*., 2002)], Okihiro syndrome [Duane retraction syndrome with radial ray anomalies and deafness, caused by mutations of *SALL4* (Al-Baradie *et al*., 2002; Kohlhase *et al*., 2005; Sakaki-Yumoto *et al*., 2006)], and congenital fibrosis of the extraocular muscles [caused by mutations of *PHOX2A* (Nakano *et al*., 2001; Bosley *et al*., 2006)].

Disorders of cerebellar foliation are poorly understood. They appear to be clinically asymptomatic when minor (abnormal orientation of vermian fissures) but may be associated with developmental delay when more extensive (Demaerel, 2002). Another disorder included in this group is cerebellar heterotopia, formed of clusters of neurons that typically lie within the white matter of a cerebellar hemisphere (Friede, 1989; Norman *et al*., 1995; Patel and Barkovich, 2002). These are most commonly seen in syndromes (especially trisomy 13) and in association with cerebellar cortical dysplasia (heterotaxias or clefts, see Group IV), but may be seen as isolated anomalies and therefore are included in Group III rather than Group IV.

Group IV. Defects secondary to combined hypoplasia and atrophy in putative prenatal onset degenerative disorders

The final group of defects is composed of progressive disorders in which the cerebellum is already small at birth and subsequently undergoes further atrophy (Table 9). The two best known disorders that fall into this category are the pontocerebellar hypoplasias (PCH) (Barth *et al*., 1990, 1993; Rajab *et al*., 2003; Patel *et al*., 2006; Barth 2007*a*; Hevner, 2007; Leroy *et al*., 2007;) and the congenital disorders of glycosylation (CDG), especially CDG type 1a (CDG1a, formerly known as carbohydrate deficient glycoprotein syndrome) (Kier *et al*., 1999; de Lonlay *et al*., 2001; Drouin-Garraud *et al*., 2001; Freeze, 2001; Miossec-Chauvet *et al*., 2003; Giurgea *et al*., 2005). Five types of PCH have been described in the literature, although it now appears that types 2 and 4 may lie along the same continuum, with type 4 having more serious clinical and pathological manifestations (Barth *et al*., 2007*a*; Hevner,

Figure 12 Molar tooth malformation in patient with ataxia, developmental delay, and nephronophthisis. (**A**) Sagittal T_1-weighted image shows a thin isthmus (large arrows) and a small vermis (small arrows) with abnormal foliation. (**B**) Axial T_2-weighted image shows large, horizontal superior cerebellar peduncles (black arrowheads) and midline vermian cleft (white arrows).

2007). All have a small brain stem and cerebellum from birth (Fig. 15), with the vermis relatively less affected than cerebellar hemispheres. Type 1 has spinal motor neuron loss; type 2 is characterized pathologically by normal spinal motor neurons and clinically by chorea/dystonia; type 3 has absence of dyskinesias, optic atrophy, and linkage to chromosome 7q11-21; types 4 and 5 have C-shaped inferior olivary nuclei with relative vermian sparing in type 4 (Hevner, 2007). Although the cerebellar malformation in both PCH and CDG1a are commonly referred to as 'hypoplasia', pathologic studies have shown the cerebellum to exhibit a combination of hypoplasia and atrophy (Norman *et al*., 1995; Pascual-Castroviejo *et al*., 2006; Barth *et al*., 2007*a*). This observation suggests that the causative gene(s) are important both for cerebellar neuronal development and for postmitotic neuronal survival (Hevner, 2007). In support of this concept, the authors have seen sequential MRI studies of several affected patients with PCH and CDG1a in whom the cerebellum was small at birth and underwent further atrophy postnatally. Thus, these disorders are classified in group V.

Figure 13 Horizontal gaze palsy with progressive scoliosis secondary to *ROBO3* mutation. Axial T_2-weighted image shows midline pontine dorsoventral cleft (arrows) caused by lack of midline crossing of axons.

The other major disorders in this group are unilateral cerebellar hypoplasia and cerebellar cortical dysplasia [also called cerebellar polymicrogyria and cerebellar heterotaxia (Friede, 1989; Norman *et al*., 1995; Soto-Ares *et al*., 2002; 2004)]. Both disorders are most often detected incidentally on neuroimaging studies for patients with unrelated complaints (Fig. 16) (Boltshauser *et al*., 1996; Patel and Barkovich, 2002; Kilickesmez *et al*., 2004; Poretti *et al*., 2009). If assessed carefully, these patients typically have abnormal foliation (Soto-Ares *et al*., 2004) or clefts (Poretti *et al*., 2008) in the affected hemisphere; thus these conditions are considered together. Affected patients are typically asymptomatic or minimally symptomatic and, typically, no associated abnormalities are found elsewhere in the brain (Friede, 1989; Norman *et al*., 1995; Soto-Ares *et al*., 2004; Poretti *et al*., 2008). Familial cases have not been reported and some patients have been found to have associated destructive lesions such as schizencephaly (Poretti *et al*., 2008). Many authors, therefore, have postulated that these

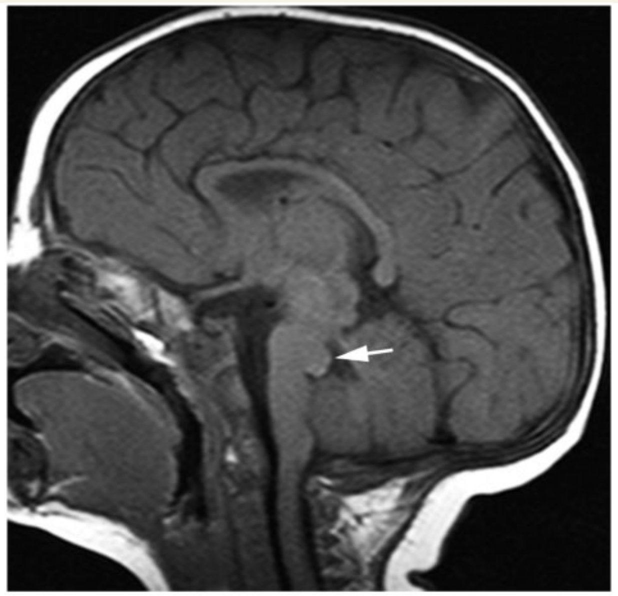

Figure 14 Pontine tegmental cap dysplasia. Sagittal T_1-weighted image shows a small ventral pons and a dorsal tegmental 'cap' (arrow) that is characteristic of the malformation. Diffusion tensor imaging studies show that the cap is composed of highly anisotropic structures, likely axons, running transversely across the dorsal aspect of the pons.

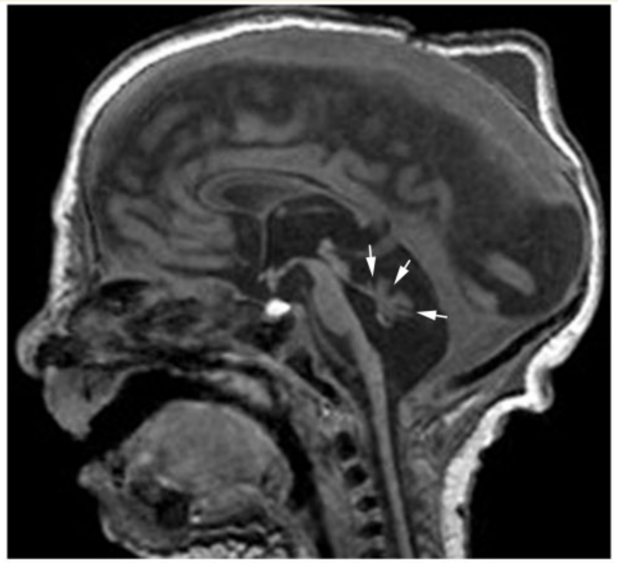

Figure 15 Pontocerebellar hypoplasia type 1. Sagittal T_1-weighted image shows very small brain stem and cerebellum in this hypotonic, encephalopathic neonate. Note prominent cerebellar fissures (arrows), suggesting atrophy that started prenatally.

Figure 16 Unilateral cerebellar hypoplasia/dysplasia. Axial T_1-weighted image shows a small right cerebellar hemisphere with a large cleft (arrows) and abnormal folial pattern. Such lesions are often associated with prenatal cerebral and cerebellar injuries and, therefore, are classified as having putative prenatal onset.

are the result of prenatal injury (Friede, 1989; Norman *et al*., 1995; Boltshauser *et al*., 1996; Kilickesmez *et al*., 2004; Poretti *et al*., 2008, 2009). In support of this concept, the authors have been referred several cases in which focal cerebellar cortical dysplasia, usually associated with hypoplasia of the affected hemisphere, developed after a second trimester or early third trimester prenatal cerebellar haemorrhage that was detected on routine obstetrical sonography and confirmed by foetal MRI.

Discussion

This classification organizes malformations of the midbrain and hindbrain into a logical system based, as much as possible, upon known embryological events and genetic mutations from work in humans and animal models. As the genetics and embryology of mid-hindbrain development are still being elucidated, this classification is far from complete. Nonetheless, it brings some order to a very difficult and confusing group of malformations and can continue to be used as a framework as our knowledge of developmental process and genetics evolves.

This classification might be criticized for some of the assumptions that have been made in the categories selected. Why are some groups based upon known embryologic processes while others are based upon whether the processes are well localized or not? The answer is that this method of grouping gives maximum flexibility to the classification. As understanding of general

Table 8 **Group III. Localized brain malformations that significantly affect the brainstem and cerebellum (pathogenesis partly or largely understood, includes local proliferation, cell specification, cell migration and axonal guidance)**

Defects	Examples	Comments and references
III.A. Multiple levels of mid-hindbrain	Mouse Mouse mutants • Sall4$^{+/-}$ - Hoxb1$^{-/-}$ Human by genotype • CHN1$^{-/-}$ Duane retraction syndrome • SALL4$^{+/-}$ » Duane radial ray syndrome, Okihiro syndrome • PHOX2A$^{+/-}$ » Congenital fibrosis of extra-ocular muscles • ROBO3$^{+/-}$ » Horizontal gaze palsy with progressive scoliosis Human by phenotype • Diffuse brainstem hypoplasia	(Nakano *et al*., 2001; Al-Baradie *et al*., 2002; Kohlhase *et al*., 2002, 2005; Holve *et al*., 2003; Jen *et al*., 2004; Bosley *et al*., 2006, 2008; Chan *et al*., 2006; Michielse *et al*., 2006; Sakaki-Yumoto *et al*., 2006; Warren *et al*., 2007)
III.B. Midbrain malformations	Human by phenotype • Midbrain dysgenesis with open clefts (ventral, dorsal with dorsoventral shortening)	Barkovich, unpublished
III.C. Rhombomere 1 including cerebellar malformations		
III.C.1. Cerebellar HET	Cb white matter heterotopia, usually associated with overlying Cb cortical dysgenesis	(Rorke *et al*., 1968; Patel and Barkovich 2002)
III.C.2. Cerebellar foliation anomalies	Human by phenotype • Refer to recent classification	(Demaerel 2002)
III.C.3. Cerebellar cell specification anomalies	Human by phenotype • Lhermitte Duclos syndrome	
III.C.4. Cerebellar hemispheric duplication	Human by phenotype • Duplication of cerebellar hemisphere and ipsilateral ear	(Jackson *et al*., 1990)
III.D. Pons malformations	Human by phenotype • Pontine tegmental cap dysplasia • Pontine dysgenesis with open clefts (ventral, dorsal with dorsoventral shortening)	(Barth *et al*., 2007*b*; Jissendi-Tchofo *et al*., 2009)
III.E. Medulla malformations	Human by phenotype • Medullary tegmental cap, always associated with cerebral callosal agenesis/hypogenesis. Suspected axonal midline crossing defects.	Barkovich, unpublished

processes in hindbrain development increases, the categories can be modified, and as understanding of the pathophysiology of individual disorders increases, those disorders can be moved to more appropriate groups. Why propose a classification now, instead of waiting until the processes are better understood? We contend that the presence of a logical classification is essential to the investigation of disorders. Classifications, even early ones, bring groups of disorders from the realm of chaos, where every case differs from every other case, to science, where the complexity of nature is reduced to a more comprehensible form. Placing a malformation in a certain group will elicit testing to see whether it belongs in that category; if not, the classification is flexible enough that it can be moved to a more appropriate one.

This classification may also be criticized for some of its details, such as the categories to which certain malformations are assigned. Why are some cerebellar hypoplasias included in Group I, while others are in Groups IV? Cerebellar hypoplasia can be the result of many different processes, starting with patterning of the developing neural tube and progressing all the way to increased apoptosis due to abnormal late migration of granule cells [granule cells undergo apoptosis if Purkinje cells have not migrated normally to their end location (Wetts and Herrup, 1982; Wallace, 1999; Kenney *et al*., 2003; Hoshino, 2006)]. In order to treat the potential causes, malformations with cerebellar hypoplasia need to be ‘split’ based upon the pathophysiology of the hypoplasia. By separating the different types of this disorder, we take the first step in making this complex diagnosis more comprehensible.

How can the authors justify the assumptions they have made in creating this classification? Any useful model is based upon some assumptions. Indeed, Sarnat uses a number of assumptions in assigning malformations to his molecular genetic classification of malformations (Sarnat, 2000). 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 another group or, perhaps, a new group. Indeed, 5 years ago no one would have suggested classifying Joubert syndrome as one of

Table 9 Group IV. Combined hypoplasia and atrophy in putative prenatal onset degenerative disorders

Defects	Examples	Comments and references
IV.A. Pontocerebellar hypoplasia (PCH)	Human by genotype • RARS2$^{-/-}$ mutation spectrum » PCH with respiratory chain defects • TSEN2$^{-/-}$ mutation spectrum • TSEN34$^{-/-}$ mutation spectrum • TSEN54$^{-/-}$ mutation spectrum » PCH type 2 with infantile dyskinesia, postnatal microcephaly, seizures, and » PCH type 4 with respiratory insufficiency and neonatal death (congenital olivopontocerebellar atrophy) Human by phenotype • PCH type 1 with infantile spinal muscular atrophy (excluded from 5q SMA locus) • PCH type 5 with hypocellular vermis, fetal seizures • Progressive encephalopathy with hypsarrhythmia and optic atrophy	PCH defined as prenatal onset degeneration and no recognized metabolic defect, and recognized by imaging due to cerebellar hemispheres more severe than vermis (Goutieres *et al*., 1977; Barth *et al*., 1990; Albrecht *et al*., 1993; Barth *et al*., 1995; Rudnik-Schoneborn *et al*., 1995; Hashimoto *et al*., 1998; de Koning *et al*., 1999; Muntoni *et al*., 1999; Barth 2000; Chaves-Vischer *et al*., 2000; Grellner *et al*., 2000; Ryan *et al*., 2000; Rudnik-Schoneborn *et al*., 2003; Patel *et al*., 2006; Barth *et al*., 2007*a*; Edvardson *et al*., 2007; Hevner, 2007; Budde *et al*., 2008)
IV.B. Mid-hindbrain malformations with CDG groups	Human by gene (and biochemical defect) • CDG type 1a, phosphomanomutase deficiency » PMM2$^{-/-}$ • CDG type 1c, glucosyltransferase deficiency » ALG3$^{-/-}$	Also see group I.B.2.b. (Marquardt and Denecke 2003; Aronica *et al*., 2005; Pascual-Castroviejo *et al*., 2006)
IV.C. Other metabolic disorders		
IV.D. Cerebellar hemisphere hypoplasia (rare, more commonly acquired than genetic)		Usually associated with Cb cortical dysgenesis [cerebellar polymicrogyria (Friede 1989), cerebellar heterotaxia (Rorke *et al*., 1968)]. Most are likely due to prenatal disruption or injury in preterm neonate (Poretti *et al*., 2008, 2009).

a group of multisystemic disorders caused by defects in ciliary proteins. Some disorders that are listed separately may have to be combined, while others that are listed as a single disorder may have to be divided into multiple groups. Discoveries may result in the creation of new groups and elimination of others. Indeed, the framework of the classification will probably need modification as new aspects of mid-hindbrain development are discovered. The strength of this classification system is that it has to flexibility to allow changes in both its framework and its listings with periodic updates as new discoveries necessitate change.

Why do the authors classify some disorders by genotype and others by phenotype? Ultimately, we hope that all malformations will be classified by genotype or disrupted embryologic step. Currently, however, our understanding of the genetic/embryologic causes of many of these disorders is not advanced enough to create such a sophisticated classification. Therefore, we have classified by genotype/embryology those malformations for which the cause is adequately understood; the more poorly understood malformations are classified by clinicoradiologic phenotype. We anticipate that number classified by genotype will increase in subsequent revisions.

Other classification systems of mid-hindbrain or cerebellar malformations have been proposed (Patel and Barkovich, 2002; Parisi and Dobyns, 2003), but have not been widely accepted by practicing neurologists and geneticists, possibly because there was no unifying thread tying together disorders within the same group. This classification attempts to rectify that problem by classifying the malformations according to the underlying processes affected. This allows the classification to grow with the knowledge of embryology and genetics that is the source of its structure. The multitude of recent advances in this understanding has brought the state of the art to the point where this genetic-embryological classification is now feasible.

This classification is not restricted to malformations restricted to the midbrain-hindbrain. To do so would be unrealistic as the developmental processes in the forebrain and mid-hindbrain share so many genes and gene products that it is nearly inevitable that the supratentorial compartment or other organs will be affected in some way when an infratentorial structures develops abnormally. Indeed, in many of these disorders, the supratentorial malformation may be the first one discovered, with the infratentorial malformation only being identified later. Discovery of the infratentorial malformation may allow a more refined classification of the overall malformation complex, however. Indeed, discovery of cerebellar abnormalities similar to those in dystroglycanopathies in patients with *GPR56* mutations led to the suggestion that the mutant protein is associated with glycosylation defects (Ke *et al*., 2008).

In summary, a developmentally based classification of midbrain-hindbrain malformations is proposed in this manuscript in an attempt to organize these disorders for better clinical understanding and guidance of future research. It is hoped that this classification helps to clarify what is known (and what is not) about normal and abnormal development of these structures and that it may help to guide future studies.

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