

Published in final edited form as:

Curr Opin Neurobiol. 2008 February ; 18(1): 12–19.

Cerebellar Development and Disease

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Recent Advances

The molecular control of cell type specification within the developing cerebellum as well as the genetic causes of the most common human developmental cerebellar disorders have long remained mysterious. Recent genetic lineage and loss-of-function data from mice have revealed unique and non-overlapping anatomical origins for GABAergic neurons from ventricular zone precursors and glutamatergic cell from rhombic lip precursors, mirroring distinct origins for these neurotransmitter-specific cell types in the cerebral cortex. Mouse studies elucidating the role of *Ptf1a* as a cerebellar ventricular zone GABAergic fate switch were actually preceded by the recognition that *PTF1A* mutations in humans cause cerebellar agenesis, a birth defect of the human cerebellum. Indeed, several genes for congenital human cerebellar malformations have recently been identified, including genes causing Joubert syndrome, Dandy-Walker malformation and Ponto-cerebellar hypoplasia. These studies have pointed to surprisingly complex roles for transcriptional regulation, mitochondrial function and neuronal cilia in patterning, homeostasis and cell proliferation during cerebellar development. Together mouse and human studies are synergistically advancing our understanding of the developmental mechanisms that generate the uniquely complex mature cerebellum.

Introduction

The basic circuitry of the mature cerebellum has been known for more than one hundred years, however, the developmental mechanisms that generate this complexity have only begun to be elucidated much more recently. The study of spontaneous and targeted mutations in mice which cause congenital ataxias has been fundamental to this progress. More recently, the use of powerful new genetic fate mapping technology in cerebellar mutant mice has driven many of the new molecular insights of cerebellar development. Concurrently, multiple human cerebellar malformations have been delineated due to improvements in neuroimaging and improved classification of these disorders. This has fueled the identification of several disease genes leading to a new molecular classification of these disorders and permitted construction of mouse models to delineate the underlying pathogenesis. Together, mouse and human genetic approaches are synergistically driving significant progress towards an improved understanding of the basic mechanisms of cerebellar development.

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Overview of cerebellar development and recent findings in mice

Cerebellar morphogenesis

The cerebellum arises from dorsal rhombomere 1 of the anterior hindbrain and is positioned along the anterior/posterior axis of the neural tube by Fgf and Wnt signals from the isthmic organizer located at the mid-hindbrain junction [1]. The developing cerebellum is also influenced by the adjacent fourth ventricle roof plate, which secretes Bmp, Wnt and retinoic acid [2,3] (Figure 1A). Mouse fate mapping experiments have shown that during early embryogenesis, there is a 90 degree rotation of dorsal rhombomere 1 which converts the rostral-caudal axis of the early neural tube into the medial-lateral axis of the wing-like bilateral cerebellar primordia [4]. As neurogenesis progresses, the bilateral primordia fuse on the dorsal midline over the fourth ventricle to establish the medial vermis and lateral cerebellar hemispheres [5].

Cerebellar neurons are generated from two anatomically and molecularly distinct progenitor zones within the primordia or cerebellar anlage. These are the cerebellar ventricular zone (VZ), expressing the bHLH factor Ptf1a, and the more dorsally located rhombic lip (RL), expressing the bHLH factor Math1 (Figure 1A). Newly differentiating neurons, including cerebellar Purkinje cells, are post-mitotic as they leave the VZ and migrate radially within the developing anlage. In contrast, cells exiting the RL migrate over the anlage forming an external layer of cells that continue to proliferate. Granule neuron progenitors within this external granule layer (EGL), are driven to proliferate through reception of a mitotic Shh signal received from the underlying differentiating Purkinje cells within the anlage (Figure 1B). Extensive cell interactions and inward radial migration of EGL cells to form the IGL, are required to achieve the final structure of the mature cerebellum [6]

Distinct origins for GABAergic and glutamatergic cerebellar neurons

Recent loss of function and fate mapping experiments have demonstrated that Ptf1a and Math1 are not only useful markers for each cerebellar progenitor zone, these transcription factors are also essential for the generation of correctly specified progenitors within their respective germinal zones. In the absence of Ptf1a, cerebellar VZ fails to generate all of the known GABAergic cerebellar neuronal subtypes including Purkinje cells (PCs), stellate and basket cells and a subset of deep cerebellar neurons, which constitute the main outflow tract of the cerebellum [7,8]. Fate mapping of Ptf1a+ cells in wild-type mice demonstrates that Ptf1a+ VZ cells are normally fated to produce all of these GABAergic cerebellar cell types and thus, their loss is caused by a primary failure of the VZ to produce appropriate neurons in the absence of Ptf1a. Fate mapping in Ptf1a^{-/-} mutants also demonstrates that some mutant cerebellar VZ progenitor cells aberrantly migrate and express typical RL markers such as Math1, Reelin, and Zic1/2, indicating a transformation of the mutant cerebellar VZ descendents to the adjacent RL cell fates. This suggests that the GABAergic fate choice in the cerebellum is based upon a relatively simple genetic switch [9].

It has long been known that the cerebellar RL expressing Math1, is the source of all cerebellar granule neurons [10,11]. Recent genetic fate mapping of Math1+ cells, combined with newly developed cerebellar slice culture assays have completely revolutionized our understanding of the cerebellar RL. Surprisingly, the Math1+ RL gives rise not only to glutamatergic granule neurons, but to all known glutamatergic neurons of the cerebellum. These include both unipolar brush cells, which serve as a relay cell amplifying the excitatory effects of mossy afferent fibers on granule cells [12], as well as the glutamatergic subset of deep cerebellar nuclei neurons, [13-18] (Figure 1A). Thus, the well ordered cellular organization of the mature cerebellum is achieved through the bipartite origins of its constituent neurons. Despite the complexity of the final mature structure, the cerebellum is not that different from the developing spinal cord and

telencephalon, where distinctly ordered progenitors along the dorsal/ventral axis of the neural tube give rise to cells of distinct neurotransmitter phenotypes [18].

In contrast to the apparent switch in cell-fate *Ptf1a* $-/-$ mutants, there is no evidence that *Math1* $-/-$ cells transform their cell fate. In *Math1* $-/-$ mutants, the rhombic lip still forms, but there is failure to produce granule neurons. As a result, there is failure to generate the EGL [19]. The new fate mapping data reveals that all other *Math1*⁺ lineage cells also fail to be generated [13,14]. Thus, *Math1* is not required for the formation of the RL or specification of neurotransmitter identity. Based on inducible fate mapping with *Math1*-CreER^{T2} mice, recent studies have even more surprisingly demonstrated that *Math1*⁺ cells are not the definitive stem cell population of the rhombic lip. Rather, *Math1*⁺ progenitor cells are continuously induced from a RL stem cell population that has yet to be identified [14].

So what are the mechanisms that segregate the VZ and RL? Recent studies have determined that both RL induction and *Math1* expression is dependent on Bmp-derived signals from the adjacent roof plate [2,20]. Further, the roof plate Bmp signal is countered by antagonistic Notch1 activity within the cerebellar ventricular zone [21]. Thus, antagonism between the Notch and BMP signaling pathways regulates the differentiation of cerebellar progenitors throughout the period of cerebellar neurogenesis.

Human congenital ataxias and their causes

The identification of *Ptf1a* as a major player in cerebellar neurogenesis has been a major recent advance in cerebellar developmental biology. Interestingly, *Ptf1a* (a gene well-known for its role in pancreas development [22]), initially came to the attention of cerebellar biologists through human genetic analysis. Mutation in the *PTF1A* gene was first identified in a large family segregating both cerebellar agenesis and neonatal diabetes [23]. Subsequent work on this gene in mice revealed its critical role in cerebellar GABAergic neuronal specification and also revealed that the complete cerebellar agenesis phenotype seen at birth in both humans and mice, is actually a secondary phenotype. In the absence of *Ptf1a*, the failure to generate GABAergic neurons secondarily leads to massive pre-natal death of all cerebellar glutamatergic neurons since their GABAergic synaptic partners are not present [24]. Together, the *Ptf1a* studies highlight the synergy between human and mouse genetics and suggest that human cerebellar congenital ataxias can greatly inform our understanding of the basic genes and mechanisms driving cerebellar development.

Overview of human congenital ataxias

Cerebellar agenesis is one many human congenital ataxias. These are a group of conditions that present in the first few years of life with motor disability, muscular hypotonia and incoordination, and impaired development. Characteristically, such patients display some degree of cerebellar malformation that typically involves the vermis, and which may accompany other developmental brain abnormalities and other non-CNS developmental abnormalities. Brain imaging studies have thus become a key element in distinguishing each malformation and has allowed for both clinical and genetic delineation of several distinct syndromes (Figure 2). Many of the newly identified causative genes have not previously been implicated in cerebellar development. The subsequent generation of related mouse models is just now beginning to illuminate many new aspects of cerebellar developmental biology.

Joubert Syndrome and related disorders

Joubert syndrome and related disorders (JSRD) are a group of recessively inherited conditions that are characterized clinically by congenital ataxia, hypotonia, episodic breathing dysregulation, and mental retardation [25]. The signature feature of this group of disorders is the “molar tooth” sign. This sign is a specific malformation of the brainstem, cerebellum and

the cerebellar peduncles, which together, give the appearance of a tooth-like shape in axial MRI images at the level of the midbrain-hindbrain junction (isthmus) [26]. (Figure 2). It has been recognized that many patients with Joubert syndrome identified by brain imaging studies, also have retinal dystrophy and nephronophthisis (renal fibrocystic disease), two conditions related to defective function of primary cilia, cellular appendages of unclear function. Several recent proteomics and bioinformatics studies have identified lists of candidate cilia-functioning proteins [27]. This data, together with availability of large, consanguineous families segregating JSRD, has sped the discovery of several of the responsible JSRD genes. Currently, there are seven genetic loci that have been mapped for the various subtypes of Joubert syndrome, and the first five genes have been identified. These include *Ableson-helper integration-1 (AHI1)*, *Nephrocystin-1 (NPHP1)*, *Centrosomal protein-290 (CEP290)*, *Transmembrane protein 67 (TMEM67)* and *Retinitis pigmentosa GTPase regulator-interacting protein-like (RPGRIP1L)*. Each of the genes encodes a modular scaffolding protein without clear enzymatic domains, but sharing several protein-interaction domains of unknown function, suggesting that they may be part of a signaling complex [28-36]

The Joubert syndrome connection with cilia

Although the function of JSRD proteins remains largely unknown, recent evidence suggests roles in either mediating the assembly/stability of cilia or mediating cargo transport within cilia. When tested directly, at least three of the encoded proteins, NPHP1, CEP290 and RPGRIP1L have demonstrated localization to the basal body or cilium [32,35-37], further suggesting a role at the cilium or basal body. Remarkably, *CEP290* was concurrently identified as mutated in the *rd16* mouse [38] and rdAc cat [39] both models of retinal dystrophy. In these models there is failure to transport rhodopsin to the photoreceptor outer segment and of disk morphogenesis. Since the photoreceptor outer segment is a giant modified cilium, the genetic evidence suggests a defect in ciliary function. Similarly, there is failure to transport G proteins into the cilia of olfactory sensory neurons *rd16* mutant mice resulting in anosmia [40]. Finally, one JSRD patient with a proven *CEP290* mutation displayed complete *situs inversus*. Together, these data suggest a link between JSRD and other ciliopathies [41]. But what could the role of cilia proteins be in the developing cerebellum?

In the developing cerebellum, primary cilia have been identified ultrastructurally in both Purkinje cells and granule cell progenitors [42,43]. Indeed, primary cilia are appendages found on most eukaryotic cells, and are defined by a membrane surrounded structure with a 9+0 or 9+2 microtubule structure and a basal body (centrosome) at the base. Primary cilia are differentiated from motile cilia found in many anatomic locations (Henson's node, respiratory epithelium, sperm cerebral ependyma), which display a patterned beating movement to produce fluid flow. The function of primary cilia is just now coming to the forefront of science, with the recent discovery of evolutionary conservation of many of the factors required for retrograde and anterograde transport in lower ciliated organisms.

The current hypothesis is that JSRD represent primary disorders of ciliary transport within cellular primary cilia in the developing cerebellum. This hypothesis is supported by analysis of mice with conditional mutations in the *Kif3a* and *IFT88* genes which encode intraflagellar transport proteins that are required for cilia formation and maintenance. These mice have cerebellar morphological defects that mirror those seen in JSRD. Mechanistically, conditional loss of *Kif3a* and *IFT* in the developing mouse cerebellum results in the failure of Shh-dependent proliferation of granule neuron progenitors within the developing cerebellar external granule layer [44,45] (Figure 1B). Since cilia are required to process both Shh and Wnt signals in a range of cell types [46-49], it is hypothesized that the JSRD genes encode mediators of these signal transduction pathways at the primary cilium and that the primary defect in JSRD is compromised granule cell proliferation which in turn, leads to significant cerebellar

hypoplasia. Axonal migration defects causing the distinctive “molar tooth” sign may also be caused by ciliary defects, however, until JSRD gene-specific knock-outs are available, these hypotheses cannot be directly tested.

Dandy-Walker malformation and Cerebellar Vermis Hypoplasia

Dandy-Walker malformation (DWM) is the most common congenital malformation of the human cerebellum. DWM is characterized by a severely hypoplastic cerebellar vermis which is rotated away from the brainstem and a significantly enlarged fourth ventricle in an enlarged posterior skull [50,51]. Although there is cerebellar hypoplasia, DWM is not associated with the “molar tooth” sign of JSRD and in contrast to JSRD, DWM very rarely segregates in large and has a very low recurrence risk families [52] [53]. The identification of rare patients with chromosomal abnormalities has opened the door to DWM gene characterization.

The first DWM causative genes were identified by physical mapping of interstitial deletions of chromosome 3q24 (del3q24) in several DWM patients [54]. This region encompasses the adjacent *ZIC1* and *ZIC4* genes, important members of the small *Zinc finger in cerebellum* family of transcription factors. Mice with heterozygous deletion of the orthologues of these two linked transcription factors have a phenotype which resembles human DWM. These mutants provide the first model to delineate the pathogenesis of DWM. Since Zic proteins interact with Gli proteins, which are obligate downstream components in Shh signal reception, it has been hypothesized that Zic proteins modulate Shh signaling [55] [56,57] and may be involved in Shh-regulated EGL proliferation. The role of *Zic4* is not well understood, but *Zic1* activity is required to maintain EGL cells in a progenitor state [57,58], although a direct role in the reception of Shh signaling has not been established. A diminishment in Shh-dependent granule neuron progenitor proliferation in *ZIC1/4*-dependent DWM may account for the cerebellar hypoplasia seen in these DWM patients, however, Zic functions that are Shh-independent may also contribute to the DWM phenotype [59,60], distinguishing DWM from JSRD. The study of *Zic* mouse models is ongoing, as is the search for additional human DWM causative genes [61].

The del3q24 DWM human phenotype is extremely variable ranging from classic DWM to mild cerebellar vermis hypoplasia (CVH) – a small cerebellar vermis that is not accompanied by enlargement of the fourth ventricle or enlarged posterior skull that is seen in classical DWM [54]. This suggests that CVH can represent one end of phenotypic spectrum with the same molecular pathogenesis as DWM. However, it is also clear CVH can also be distinct from DWM. For example, mutations in *Oligophrenin 1* (*OPHN1*), a widely expressed gene encoding a rhoGAP protein, cause X-linked mental retardation and CVH, but never DWM [62-64]. *In vitro* and *in vivo* experiments have demonstrated a role for *Ophn1* in dendritic spine morphogenesis in hippocampal neurons in mice, although no gross cerebellar anatomical abnormalities were observed in *Ophn1* mutant mice [65,66]. Thus, the basis of human *OPHN1*-dependent CVH remains obscure.

Developmental degenerative disorders

Numerous degenerative disorders of the mature cerebellum, known as Spinal Cerebellar Ataxias (SCA), have been described in humans, many of which are caused by expanded CAG trinucleotide repeats leading to the progressive degeneration of Purkinje cells [67]. An intriguing recent paper demonstrates that compromising Purkinje cell development, by expressing a toxic transgene early in development, contributes to the severity of the neurodegeneration in adult mice [68]. This data suggests an overlap between development and degeneration, and that the eventual timing of the onset of degeneration is actually determined during pre-natal life. Apparently, we can no longer think of development and degeneration as distinct entities. This is certainly the case with *PTF1A* mutations and cerebellar agenesis, as

discussed above. A number of additional human cerebellar developmental degenerative disorders have been recognized and have been classified as Pontocerebellar hypoplasia (PCH). PCH is characterized by the progressive atrophy of the ventral pons, inferior olive and cerebellum, with onset during neonatal cerebellar development, but continuing after birth. At least three subtypes exist based on clinical and pathological features [50,69]. The first PCH gene has recently been reported as a loss-of-function of *RARS2*, encoding mitochondrial arginine-transfer RNA (tRNA) synthetase. This mutation was identified in a family with non-syndromic PCH already evident at post-natal day 3 [70]. Since *RARS2* is expressed in all cells, the mechanism of the neuron-specific phenotypes remains unclear. It will be fascinating to see this discovery translate into an improved understanding for the role of mitochondria in cerebellar development and homeostasis once appropriate mouse models are generated.

Conclusions

The cerebellum plays critical roles in sensory integration, motor planning as well higher cognitive processing [71]. Despite its importance, we know surprisingly little about its development. The use of new fate mapping strategies in mice has helped define unexpected origins for unique cellular populations within the cerebellum. Defining the genetic underpinnings of some of the common causes of cerebellar malformations in humans holds the promise of improving diagnosis and prognostic information for these relatively common birth defects, as well as helping to uncover the unique molecular cues that are required for development of the cerebellum across species.

References

**Sgaier 2005

The authors used genetic fate mapping of *Engrailed1* and *Engrailed2* to determine that the vermis is produced by expansion, rather than fusion, of the thin medial primordium, which may provide an explanation as to why the vermis is particularly vulnerable to defects in cell proliferation. These elegant genetic fate mapping analyses also demonstrate how the initial anterior/posterior axis of dorsal rhombomere 1 is transformed into the medial/lateral axis of the cerebellum

*Lews 2004

One of the first papers to describe that Sonic hedgehog was produced by Purkinje cells and responsible for expansion of the granule neuron precursor population.

**Englund 2006

Described the origin of unipolar brush cells as derived from the rhombic lip. One of the first papers to present a model of cerebellar neurogenesis, in which glutamatergic and GABAergic neurons are produced from separate progenitor pools located mainly in the rhombic lip and the cerebellar ventricular zone, respectively.

**Dixon-Salizer 2004 and Ferland 2004

First reports of positional cloning of a gene for the classical type of Joubert syndrome, which turned out to be *Ahleson helper integration-1*, encoding a modular scaffolding protein of unknown function.

**Valente 2006 and Sayer 2006, Chang 2006, den Hollander 2006, Menotti-Raymond 2007

First report of mutations in the *Centrosomal associated protein 290* gene as responsible for Joubert syndrome type B, also mutated in mouse *rd16*, cat *rdAC*, and humans with retinal degeneration.

*Chizhikov 2007, Spassky 2008

These papers used several different mouse models with defective or absent cilia and found strong defects in cerebellar development primarily caused by decreased granule neuron proliferation due to defective Sonic hedgehog signaling, suggesting that defective Shh signaling is the primary cause of cerebellar defects in JSRD.

*Grinberg 2004

First report of mutations in the *ZIC1* and *ZIC4* as deleted in Dandy-Walker syndrome.

**Edvardson 2007

Reported a consanguineous Sephardic Jewish family with three patients displaying severe infantile encephalopathy associated with pontocerebellar hypoplasia and multiple mitochondrial respiratory-chain defects. This resulted in the identification of an intronic mutation in the *RARS2* gene, encoding mitochondrial arginine-transfer RNA synthetase. The authors speculate that this splicing mutation preferentially affects the brain because of a tissue-specific vulnerability of splicing machinery.

*Sillitoe and Joyner (2007)

An excellent recent review of major mechanism of cerebellar morphogenesis and circuit formation

*Chizhikov et al (2006)

Through genetic manipulation of the size of the cerebellar roof plate, the authors demonstrate that roof plate-derived signals regulate proliferation within the cerebellar anlage and are required for rhombic lip specification, establishing the roof plate as a second major signaling center in cerebellar development.

*Wilson et al (2007)

Based on extensive gene expression analysis, these authors pose the intriguing hypothesis that retinoic acid may be an important signaling molecule during late embryonic stages of cerebellar development

*Hoshino et al (2005)

The first report demonstrating that *Ptf1a* is essential for cerebellar GABAergic neuronal specification through analysis of a transgenic-insertion mutation in *Ptf1a* and *Ptf1a-cre* lineage analysis.

*Zhao et al (2007)

Although *Lhx1* and *2* are expressed in all *Ptf1a*-derived cerebellar ventricular zone descendants, the function of these transcription factors is only required in Purkinje cells as demonstrated through loss of function analysis in mice. The specificity of the mutant phenotype may be related to co-factor availability.

*Corrales (2006)

The authors demonstrate that levels of Shh signaling driving the extent of GCP proliferation accounts for the complexity of cerebellar foliation in higher vertebrates

*Sudarov and Joyner (2007)

The first detailed description of the cellular events associated with establishment of the cardinal fissures of the developing cerebellum

**Englund et al (2006)

Elegant study using embryonic cerebellar slice cultures showing a rhombic lip origin for unipolar brush cells.

*Fink et al (2006)

A transcription factor cascade involving Tbr, NeuroD and Pax6 seen in cerebral cortex interneuron development is also conserved in cerebellar rhombic lip descendants

**Pascual et al (2007)

A stunning lineage analysis demonstrating that loss of Ptf1a in cerebellar ventricular zone (GABAergic) progenitors causes a cell fate switch to more dorsal rhombic lip (glutamatergic) fates

*Baala et al (2007)

The significant phenotypic overlap between Joubert Syndrome and Meckel-Gruber syndrome can be explained by mutations in the same gene MSK3.

*Arts et al (2007) and Delous et al. (2007)

The paper identify the most recently identified gene for JSRD found through linkage analysis

*Jalali et al. (2008)

Linkage analysis in an extended pedigree segregating DWM and a posterior skull defect locates the causative locus to chromosome 2q36. The locus for an additional pedigree segregating the same phenotype, however, does not overlap, suggesting that there are multiple causes for this phenotype.

**Serra et al (2006)

No longer can we think of developmental abnormalities and Purkinje cell degenerative disorders as separate entities. Using transgenic analysis, these authors demonstrate that a developmental compromise in early Purkinje cell development advances the age of onset of SCA1-mediated Purkinje cell degeneration.

** Machold and Fishell (2007)

The authors delineate a new and critical role for Notch within the cerebellar ventricular zone. Using retroviral gain-of-function and conditional loss of function analysis in mice, they demonstrate that Notch in the cerebellar ventricular antagonizes Bmp signals from the roof plate which are required to induce the cerebellar rhombic lip. Notch signaling therefore sets a ventral limit on the size of the cerebellar rhombic lip.

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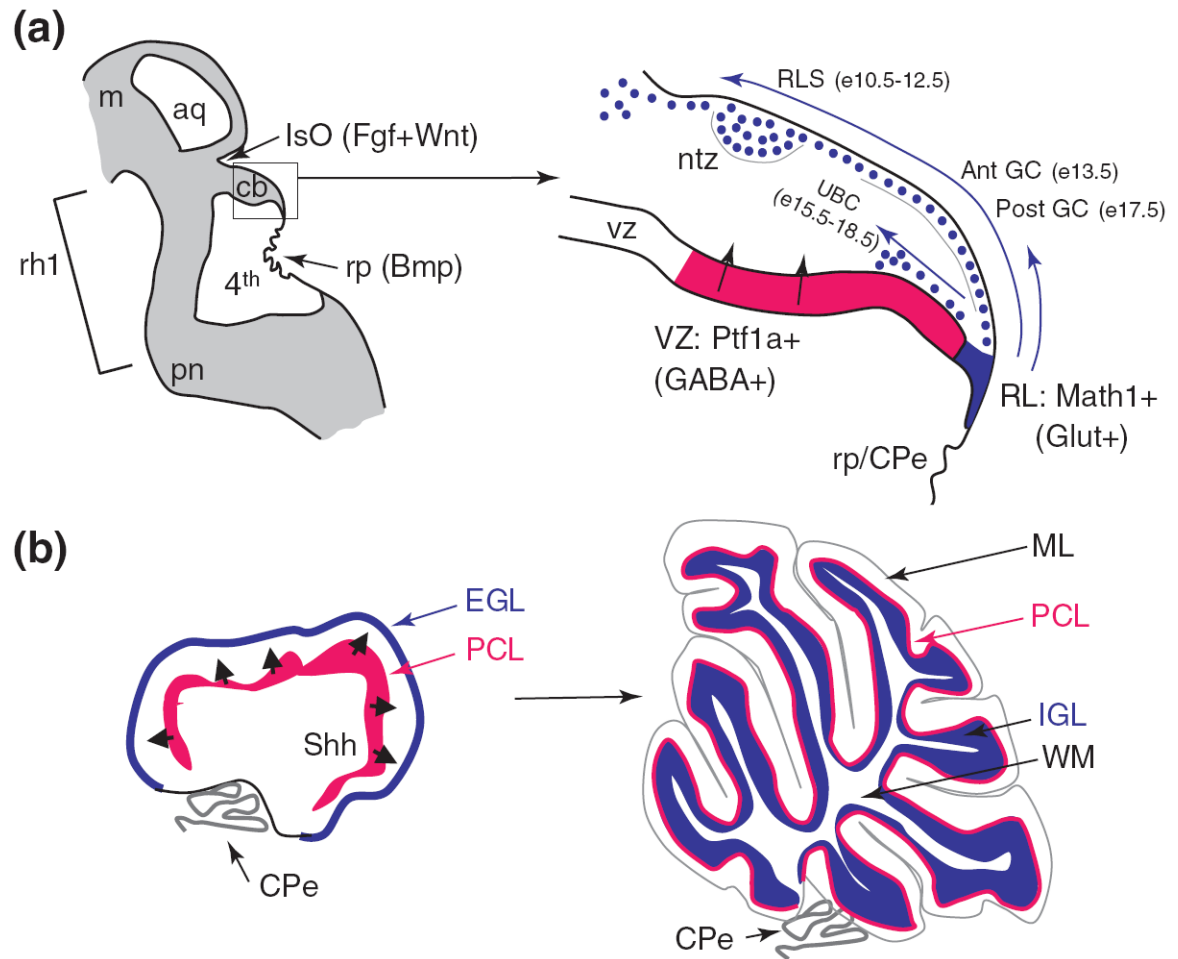


Figure 1. Overview of mouse cerebellar neurogenesis

(A) Schematic parasagittal section through the mid/hindbrain region of a mouse e12.5 neural tube. The cerebellum is a dorsal derivative of hindbrain rhombomere 1 (rh1) under the influence signaling from both the isthmus organizer and fourth ventricle roof plate. 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) is induced by Bmp signaling from the roof plate (rp) which itself differentiates into the choroid plexus (CPe). Genetic fate mapping studies have shown that Math1+ RL progenitor cells give rise to multiple glutamatergic+ derivatives in a time-dependent sequence. Early progenitors feed into the rostral migratory stream (RLS). The RLS migrates over the cerebellar anlage and gives rise to multiple brain stem precerebellar nuclei, including the pontine nuclei (pn). RLS cells next give rise to glutamatergic deep cerebellar nuclei which settle into the nuclear transitory zone (ntz). Math1+ RL cells also generate cerebellar granule cells (GC) which form the cerebellar external granule layer in an anterior to posterior temporal gradient. Unipolar brush cells (UBCs) are the final Math1+ RL population and migrate through the cerebellar white 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 cerebellar interneurons including Basket and Stellate cells. m=midbrain; aq=aqueduct. (B) Schematic midsagittal section of mouse cerebellum at day of birth. The Purkinje cell layer (PCL) is located underneath the EGL and secretes Shh which is received by EGL cells and drives their extensive proliferation such that

granule cells become the most abundant neurons in the cerebellum and in the entire brain. Upon differentiation, EGL cells migrate through the PCL layer to form the IGL of the mature cerebellum. Their trailing axons form the molecular layer (ML). Purkinje cells project into the cerebellar white matter (WM). Drawings are not to scale

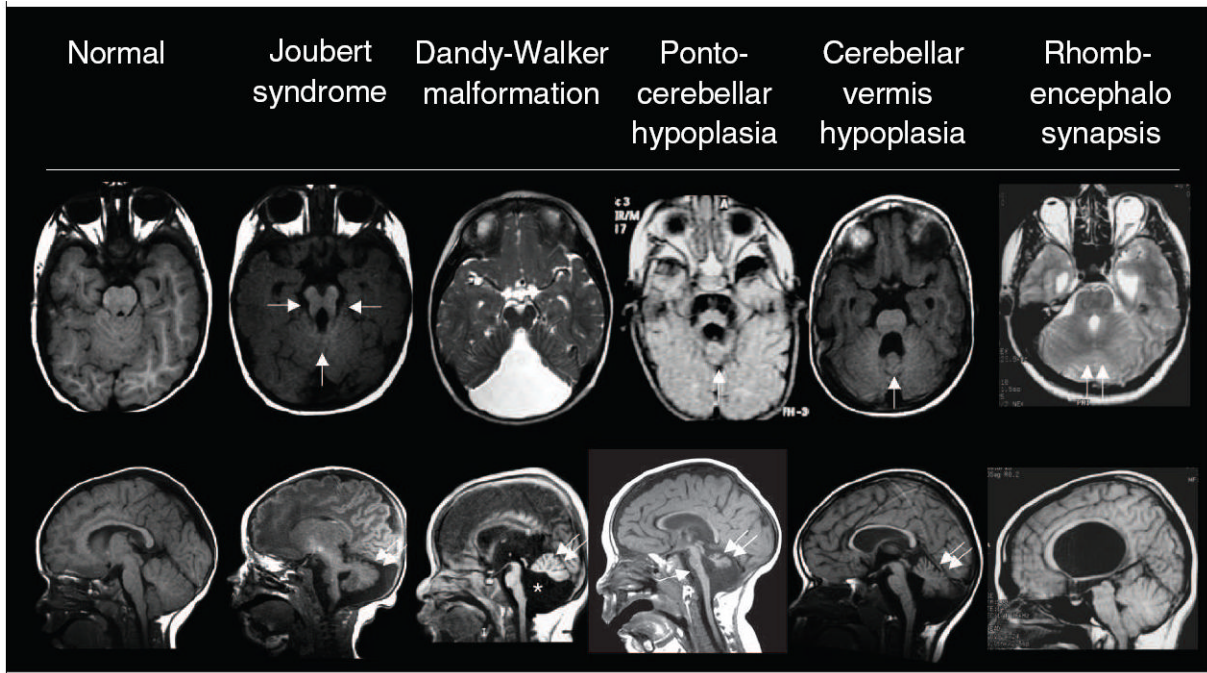


Figure 2. Spectrum of human cerebellar malformations on MRI

Top row: Axial images at the level of the midbrain-hindbrain junction (isthmus). Bottom row: Midline sagittal images. In normal, isthmus shape is relatively circular, and cerebellar vermis is full. In all of the conditions except rhombencephalosynapsis the cerebellar vermis is hypoplastic (double arrows on bottom row). In Joubert syndrome (JSRD) the isthmus takes the shape of a “molar tooth” (arrows). In Dandy-Walker malformation (DWM), the posterior fossa is full of fluid (white field) and bottom shows the cystic dilatation of the fourth ventricle (*), which is rotated anteriorly. In Pontocerebellar hypoplasia (PCH) the brainstem is also involved. Note small isthmus and vermis (arrow, top) and reduced brainstem volume (arrow, bottom). Cerebellar vermis hypoplasia (CVH) shows reduced vermis without other associated features. Rhombencephalosynapsis shows fusion of the two cerebellar hemispheres, and the vermis is replaced by this fusion. (double arrows, top).