NEUROANATOMY ASSIGNMENT

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REVIEW ON THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM

The cerebellum, which stands for “little brain”, is a structure of the central nervous system. It has an important role in motor control, with cerebellar dysfunction often presenting with motor signs. In particular, it is active in the coordination, precision and timing of movements, as well as in motor learning.

## In the last several decades, various approaches have contributed to our understanding of the molecular basis of cerebellar development. The study of spontaneous neurological mouse mutants aided many initial discoveries that are further reviewed below. Significant advances in mouse genetics have allowed for more targeted studies using engineered gene knockouts and transgenic mice.

## These mice have facilitated the examination of more subtle phenotypes such as mild behavioral abnormalities and small disruptions in cerebellar circuitry. Advances in brain imaging techniques and improvements in the classification of human cerebellar malformations have further aided the discovery of genes regulating cerebellar development. Genetics has recently enabled the identification of genes causing human pontocerebellar hypoplasia, Joubert syndrome, and Dandy–Walker malformation (DWM). When combined with studies in mouse, a variety of molecular mechanisms, including transcriptional regulation, mitochondrial function, and ciliary signaling have been implicated in homeostasis, patterning, and cell proliferation during cerebellar development.

## Concurrently, the application of new genomic techniques, which amass vast amounts of biological information, is just beginning to unravel the systems biology of the developing cerebellum. Here we discuss these issues and advocate the integrated use of human and mouse systems to further advance our knowledge of the molecular and developmental processes that form the cerebellum. In the last several decades, various approaches have contributed to our understanding of the molecular basis of cerebellar development. The study of spontaneous neurological mouse mutants aided many initial discoveries that are further reviewed below

## The Cerebellum as a Genetic System

The mature cerebellum has exquisite, stereotypical morphology, foliation, and lamination, which are consistent between individuals and highly conserved across vertebrates. At the cellular level, unlike other regions of the CNS, the cerebellum is composed of very few neuronal types, each with distinct morphology, arranged in discrete lamina, and connected in stereotypical circuits . The cerebellum has essential roles in motor coordination, but is not essential for viability. Thus, compared with other regions of the central nervous system (CNS) the cerebellum has been more amenable to genetic studies since disruptions in development, which lead to abnormal morphology or function, are readily observed in obvious neurological and behavioral phenotypes. Because of this, it has been possible to obtain a precise understanding of cerebellar development . The mechanisms deciphered from the study of cerebellar development have broad applicability to other CNS regions such as the cerebral cortex. For example, while initial insights regarding the function of the *Reelin* gene were gleaned from studying the cerebella of *reeler* mice recent studies have revealed that this gene is required for the emigration of dentate gyrus progenitors from a transient subpial zone and into the subgranular zone. Also, while *Foxc1* controls normal cerebellar and posterior fossa development by regulating secreted growth factor signals from the mesenchyme it is also required for the development of meningeal structures that in turn influence skull and cortical development.

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When combined with studies in mouse, a variety of molecular mechanisms, including transcriptional regulation, mitochondrial function, and ciliary signaling have been implicated in homeostasis, patterning, and cell proliferation during cerebellar development. Concurrently, the application of new genomic techniques, which amass vast amounts of biological information, is just beginning to unravel the systems biology of the developing cerebellum. Here we discuss these issues and advocate the integrated use of human and mouse systems to further advance our knowledge of the molecular and developmental processes that form the cerebellum.

## Developmental Insights from Mouse Cerebellar Mutants

### Spontaneous Neurological Mouse Mutants

A search of Mouse Genome Informatics (MGI) at The Jackson Laboratory reveals just over 170 spontaneous, ENU- or X-ray-induced mutant alleles with altered cerebellar function or development. Most spontaneous cerebellar mutants were identified due to their behavioral or morphological phenotypes and, as such, are severely affected. Phenotype-to-gene approaches, commonly referred to as forward genetics, enabled an unbiased search for genes involved in cerebellar development, since the phenotype indicated that the mutation by definition affected a gene important for the disrupted process. There are no prior assumptions regarding gene function. Here we highlight several classical mutants to demonstrate that they have been pivotal to our current knowledge of cerebellar development and continue to be a rich resource for the cerebellar research community.

The staggerer mutation spontaneously arose at The Jackson Laboratory in 1955 and was first described in 1962. The cerebellum of these mice is small and there is pronounced post-natal loss of Purkinje and granule cells. The discovery that parallel fiber activity is important for the pruning and refinement of climbing fiber–Purkinje cell synaptic arrangement was derived from these mutants prior to the identification of the causative deletion of retinoid-like orphan receptor alpha (Rora) in 1996. Staggerer chimeric analysis provided key evidence for the interdependence of Purkinje and granule cells during early post-natal development. Subsequent genome-wide expression analysis in staggerer mutants confirmed that Rora acts as a transcriptional regulator of Purkinje cells and regulates the secretion of sonic hedgehog (SHH), a mitogen for adjacent granule cell progenitors in the external granule layer.

The lurcher mouse, harboring a gain-of-function mutation in the delta 2 ionotropic glutamate receptor, Grid2, normally expressed in Purkinje cells, has also been an important model. The cerebellum of this mutant is hypoplastic due to severe post-natal degeneration of Purkinje, granule, and olivary neurons. The absence of Purkinje cells causes a significant reduction in the proliferation of granule cell precursors primarily due to a lack of the mitogenic effects of SHH. Other factors, such as IGF-1, FGF2, and EGF are known to act as mitogens in the cerebellum, but SHH has been shown to be over two orders of magnitude more potent. Any granule cells that are produced due to the proliferative effects of these other factors end up dying since there is a paucity of Purkinje cells with which to form synaptic contacts. Indeed, there is a linear relationship between the number of Purkinje and granule cells in the cerebellum, and in the absence of enough Purkinje cells there occurs a concomitant death of the “extra” granule cells. Thus, this mutant showed that target neurons likely provide trophic support to pre-synaptic contacts.

Leaner and weaver mice, harboring mutations in the alpha-1A calcium channel subunit gene, Cacna1a, and the potassium inwardly rectifying channel gene, Girk2, respectively, also exhibit Purkinje and granule cell death. The leaner mouse has been useful in demonstrating the role of intracellular calcium ion concentrations and neuronal apoptosis in cerebellar development. And even though Girk2 is expressed in both granule and Purkinje cells, the weaver mutation preferentially affects the former, demonstrating that some neurons are more susceptible to this particular mutation.

Not all mutations cause cerebellar cell death. The dreher (Lmx1a) mutant mouse fails to form the fourth ventricle roof plate, an essential embryonic signaling center adjacent to the developing cerebellar anlage. Loss of this transcription factor in the roof plate causes secondary mis-specification of adjacent cerebellar neurons Disruption of neuronal migration also occurs in reeler and scrambler mutants, resulting in small cerebella with no foliation and ectopic clusters of Purkinje cells beneath the granule cell layer. Disruption of the large Reelin gene, which codes for a secreted extracellular matrix serine protease, is responsible for the reeler phenotype whereas mutations in the Dab1 gene, coding for a cytoplasmic adapter protein, cause the scrambler phenotype. It appears that Reelin acts as an inhibitory signal for migration because ectopic Purkinje cells form in both reeler and scrambler . The rostral cerebellar malformation mutant contains a mutation in the Netrin receptor Unc5h3 gene that results in over-migration of granule and Purkinje cells into the midbrain and fewer cerebellar folia .Experiments with chimeras demonstrated the co-dependence of different cell types during cerebellar development as wild-type Purkinje cells exhibit inappropriate migration under the influence of Unc5h3 mutant granule cells.

Notably, there are many spontaneous and ENU-induced cerebellar mutants which remain to be characterized and are certain to add new, interesting, and likely unpredictable pieces to the puzzle of cerebellar development.

### Targeted Mouse Mutants

The advent of transgenesis and gene-targeting technology has greatly aided the discovery of genes regulating cerebellar development. Gene expression patterns initially identified many genes likely to be involved in cerebellar development. Essential roles for these genes were verified in knockout mice. For example, insights on the function of the isthmic organizer and its role in defining the cerebellar territory along the early neural tube were found from analysis of targeted alleles of Gbx2, Otx2, En1/2, Wnt1, Fgf8, and other genes.

Modern molecular genetics methods have also provided an understanding of genes that cause subtle phenotypes not likely to be found in forward genetic screens. These phenotypes affect higher order roles of the cerebellum, such as learning, memory, and synaptic plasticity. For example, targeted mutants with a deletion of Grid2 result in Purkinje cell dendrites that form reduced synaptic contacts with granule cell parallel fibers. Whole-cell patch-clamp demonstrated that mutant Purkinje cells lack long-term depression (LTD). Mice with a targeted mutation of the metabotropic glutamate receptor 1 (mGluR1) also shed light on the molecular basis of cerebellar synaptic plasticity as they showed a spatial learning deficiency and a lack of cerebellar LTD. Neuronal calcium ion concentration plays a role in synaptic plasticity through a variety of mechanisms, which include regulation of neurotransmitter release, gene transcription, and altered ion channel permeability. Mice lacking the gene for Calbindin1, an intracellular calcium-binding protein that acts as a calcium ion buffer in Purkinje cells, exhibit impaired movements only when challenged, suggesting an impairment of the cerebellum to adapt to a changing environment. Patch-clamp recordings further revealed an alteration of synaptic calcium transients in mutant Purkinje cells. Moreover, an antisense transgenic approach to diminish Calbindin1 mRNA levels demonstrated that this gene is required for the maintenance of hippocampal long-term potentiation (LTP) and spatial learning. Mice lacking the Calbindin2 gene (alias: Calretinin), which is expressed in granule cells, exhibit motor defects and increased granule cell excitability in the absence of abnormal morphology.

Current state-of-the-art mouse molecular genetics technologies now give us the ability to precisely and selectively modulate gene function. Thus, genes with essential roles throughout the developing embryo can be disrupted specifically in the cerebellum, leaving their non-cerebellar roles unaffected. Conditional gene ablation can be accomplished by the use of Cre-LoxP or other related recombinase systems, where a cell- or tissue-specific promoter drives the expression of Cre recombinase, which then excises any DNA flanked by recombinase recognition LoxP sequences. The tamoxifen-inducible Cre-LoxP system, which utilizes a fusion of Cre with an estrogen receptor ligand-binding domain, makes it possible to study gene function during a specific time and place in development . A wide variety of regulatory sequences have been identified which can drive recombinase expression to individual cell types of the cerebellum and the developing CNS (reviewed in . For example, Pcp2 regulatory sequences have been widely used to target Cre expression to Purkinje cells , whereas Atoh1 regulatory elements are often used to drive Cre expression in granule cells . These regulatory sequences can also be used to overexpress genes/alleles of interest in specific cell types. For example, the Gbx2 gene, which is critical for the placement of the mid-hindbrain junction, was ectopically expressed in the midbrain and rhombomere 1 of the hindbrain by using Cre expression driven by the regulatory elements of Engrailed1 . This study showed that Gbx2 gain-of-function in this region of the brain eliminates the expression of isthmic organizer gene Fgf8, and results in the absence of the midbrain and cerebellum at later stages.

Additional studies in mouse and other model organisms such as zebrafish, can be further utilized to understand the molecular mechanisms of cerebellar development . It is now feasible to generate specific models of human cerebellar malformations which allow for the study of underlying developmental biology of clinically important disorders.

## Advances in Cerebellar Development from the Study of Human Cerebellar Malformations

In addition to spontaneous and targeted mouse mutants, the study of human cerebellar malformations is beginning to provide new insights regarding the basic developmental principles of the cerebellum. Currently, human patient populations with congenital developmental disorders are largely underutilized in basic research but they have proven to be valuable for identifying novel, significant developmental genes. As in the mouse, disruption of human cerebellar development is often severely handicapping but not lethal, making it amenable to genetic analysis. Also similar to mice, the structure of the human cerebellum facilitates the easy identification of malformations as its morphology, foliation, and lamination are stereotypical across individuals and its morphogenesis is well understood. In conjunction with advances in imaging techniques, this allows patients to be diagnosed with malformations at early post-natal or even fetal stages. While patient populations provide a great resource for researchers, they are not often employed due to several difficulties, including a lack of routine brain imaging on patients with developmental abnormalities, genetic heterogeneity among cerebellar patients resulting in the requirement of large sample sizes, and difficulties recruiting patients. Despite these obstacles, human cerebellar malformations have been used to identify cerebellar developmental genes . Gratifyingly, mutations in human RELN cause cerebellar hypoplasia, similar to the phenotype seen in the reeler mouse , demonstrating the validity of cross species comparisons. Once genes have been identified in human cerebellar malformation syndromes, mouse models have proven essential for deciphering the underlying developmental disruptions .

QUESTION 2

GENETIC BASIS OF KNOWN CEREBELLAR DISORDERS

### Types of Human Cerebellar Malformations

Advances in imaging, genetics, and classification are enabling previously consolidated malformations to be delineated into distinct categories. Here we will discuss cerebellar vermis hypoplasia (CVH), DWM, Joubert syndrome and related disorders (JSRD), and pontocerebellar hypoplasia (PCH) .

 The defining features of these diagnoses are based on imaging criteria rather than clinical outcome, with most of these diagnoses associated with intellectual and motor disabilities. CVH is characterized by a small hypoplastic cerebellum with the vermis more affected than the hemispheres. DWM includes CVH; however, there is also an upward rotation of the cerebellar vermis that results in an enlarged fourth ventricle, and an increased size of the posterior fossa. DWM is the most common cerebellar malformation, with an estimated incidence of approximately 1 in 5,000 . CVH is also relatively common and often confused with DWM, making estimations of incidence problematic. CVH and DWM often present as sporadic cases, although there are several CVH loci with known recessive or X-linked inheritance . Mendelian inheritance for DWM is rare, and the genetics are likely oligogenic .

 In contrast, JSRD are most often autosomal recessive disorders and are rare, with a population incidence estimated to be 1/100,000 . As a group, JSRD are characterized by cerebellar vermis hypoplasia plus the presence of elongated cerebellar peduncles and a deepened interpeduncular fissure that appear as a “molar tooth” on axial brain scans. In addition, these patients exhibit axon guidance defects that include a decussation failure of the pyramidal tract and superior cerebellar peduncles. Patients with PCH exhibit a heterogeneous set of malformations characterized by hypoplasia and atrophy of the cerebellum, inferior olive, and ventral pons. This degenerative disorder often begins with embryonic atrophy of these regions.



**Magnetic resonance images (MRI) showing sagittal views of the cerebellar vermis from a subset of human cerebellar malformations. The image of a patient with cerebellar vermis hypoplasia (CVH) shows decreased vermis size that does not reach the obex, the narrowing of the fourth ventricle in the caudal medulla (white line), as occurs in normal subjects. In addition to vermis hypoplasia, subjects with Dandy–Walker malformation (DWM) also exhibit an increased posterior fossa size and an upward rotation of the vermis. The parasagittal image of a patient with Joubert syndrome shows vermis hypoplasia and an elongated superior cerebellar peduncle (white arrowhead). The plane of this off-midline image is designated with a dotted white line in the corresponding axial image. The “molar tooth” malformation of Joubert syndrome and related disorders can be seen in the axial MRI as elongated cerebellar peduncles (white arrowhead) and deepened interpeduncular fossa (black arrow) compared with a normal subject (N; inset). Subjects with pontocerebellar hypoplasia (PCH) exhibit both decreased vermis size and pontine hypoplasia (arrows). Cb cerebellum, PF posterior fossa**

### Causative Genes in Human Cerebellar Malformations

In the last decade, there has been considerable effort in defining the genetic basis of human cerebellar malformations. Causative genes include those involved in cerebellar patterning, cell fate specification, and other developmental processes

### Table 1

List of genes and suspected cellular processes that have been implicated in human cerebellar malformations (see text for discussion)

| **Cerebellar malformations** | **Implicated human genes** | **Likely disrupted process** |
| --- | --- | --- |
| Cerebellar vermis hypoplasia (CVH) | OPHN1 [[59](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R59), [60](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R60)] | Spine morphogenesis |
| Dandy–Walker malformation (DWM) | ZIC1, ZIC4 [[65](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R65)], FOXC1 [[17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R17)] | Granule cell differentiation |
|  |  |  |
| Joubert syndrome and related disorders  | AHI1 [[67](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R67), [68](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R68)], ARL13B [[69](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R69)], CCD2A [[70](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R70), [71](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R71)], CEP290 [[72](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R72), [73](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R73)], INPP5E [[74](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R74), [75](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R75)], NPHP1 [[76](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R76), [77](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R77)], RPGRIP1L [[78](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R78), [79](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R79)], and TMEM67 [[80](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R80)] | Granule cell proliferation |
|  |  |  |
| Pontocerebellar hypoplasia (PCH) | CASK [[86](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R86)], RARS2 [[88](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R88)], TSEN54, TSEN34, and TSEN2 [[89](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R89)] | Spine development, cell proliferation, tRNA splicing, cellular maintenance |

Pancreas specific transcription factor 1a (Ptf1a) was initially implicated as a basic helix–loop–helix transcription factor in pancreatic development since mice with a targeted deletion lacked pancreatic tissue . However, its role in brain development was not investigated until truncations of this gene were found to result in cerebellar agenesis in multiple families . Further investigations determined that loss of Ptf1a causes a failure to generate GABAergic cerebellar neurons in the embryonic cerebellar anlage in both human and mouse . Since Purkinje cells, which are GABAergic, are also required for the proliferation of cerebellar granule neurons, humans and mice lacking Ptf1a exhibit profound cerebellar agenesis .

Transcription factors have also been implicated in other types of cerebellar malformations. Heterozygous loss of the ZIC1 and ZIC4 genes encoding zinc finger transcription factors can cause DWM, a phenotype which is mimicked in Zic1 and Zic4 double heterozygous mutant mice . Mutations in FOXC1, a transcription factor gene located in the 6p25.3 locus, have recently been shown to contribute to human DWM . Mouse models have demonstrated that Foxc1 is developmentally expressed in the mesenchyme adjacent to the cerebellum, where it is critical for normal posterior fossa development . In addition to regulating skull development, Foxc1 controls mesenchymally expressed signaling molecules including Bmp2 and Bmp4 . Loss of these signaling molecules causes the adjacent cerebellar rhombic lip to lose Atoh1 (Math1) expression, a gene critical for normal granule cell differentiation. These findings, based on studies in both human and mice, have surprisingly implicated mesenchymal signaling as a critical regulator of early cerebellar anlage development.

Studies of JSRD patients have also provided surprising insights into new developmental mechanisms. Of the nine loci linked to JSRD, eight have been cloned and the following causative genes identified: AHI1 ,ARL13B , CC2D2A ,CEP290 , INPP5E ,NPHP1 ,RPGRIP1L [, and TMEM67 . Many of these genes are implicated in normal ciliary function and their protein products localize to the cilia or basal bodies. One such cilia-related protein is Nephrocystin, the product of NPHP1, which interacts with beta-tubulin and localizes to primary cilia . In cell culture, CEP290, centrosomal protein 290, is involved in ciliogenesis, localizes to centrioles in a microtubule-dependent manner, and regulates the microtubule network, as shown through RNAi. Furthermore, CEP290 interacts with the protein product of CCD2A both genetically and physically . Most recently, mutations in the INPP5E gene, which codes for inositol polyphosphate-5-phosphatase E, were found in patients with Joubert syndrome. While it was known that this enzyme hydrolyzes phosphatidylinositols, INPP5E was found to be localized to cilia and mutations resulted in premature destabilization of cilia after stimulation . Thus, examination of human patients led to a novel role for INPP5E in both cilia signaling and Joubert syndrome. Mutations in many components of this single biological pathway result in similar cerebellar defects. The actual purpose of cilia in the cerebellum is likely to be linked to SHH signaling. Significantly, loss-of-function mutations in murine Kif3a and Ift88—genes encoding intraflagellar transport proteins for the formation and maintenance of cilia—cause SHH-dependent proliferation defects of granule cell progenitors. This loss of SHH signaling results in cerebellar phenotypes resembling those seen in JSRD . JSRD now provide a model for how studies of human cerebellar malformations can lead to the discovery of causative genes and expand our knowledge of the pathways involved in cerebellar development.

Additional molecules have been implicated in human cerebellar malformations, which are certain to illuminate new cerebellar developmental mechanisms. Deletions of the Rho-GAP protein encoding gene Oliogphrenin-1 (OPHN1) have been found in multiple families with X-linked CVH . While Ophn1 is required for the stabilization of glutamatergic spines , it has not been implicated in regulating earlier developmental events such as cell division. Interestingly, mice with a targeted deletion of Ophn1 exhibit learning deficits and have dilated lateral and third ventricles, but their cerebellar size and morphology are normal . This suggests that the mental retardation (MR) seen in human patients may not be due to cerebellar defects. However, until the connectivity and plasticity of the mutant mouse cerebellum are examined in detail this only remains a speculation. Recently Ophn1 has been shown to facilitate clathrin-mediated endocytosis of post-synaptic vesicles, including the AMPA receptor, by repressing the RhoA/ROCK pathway . Because of this, mutant mice lack LTD in the hippocampus. Cerebellar LTD still remains to be examined.

Mutations of another molecule with a known role in synapse development have also been seen in PCH . CASK is a calcium/calmodulin-dependant serine/threonine kinase localized to synapses via membrane-associated molecules, including Neurexin. CASK also regulates gene transcription during cell proliferation . Although mouse Cask mutants have cerebellar hypoplasia, the developmental basis for this pathology has not yet been studied . Genes from the tRNA splicing pathway have also been observed to cause PCH when mutated in humans. One family has been found with three members containing mutations in the RARS2 gene, which encodes mitochondrial arginine-transfer RNA synthase . Individuals with PCH have also been found to have mutations in TSEN54, TSEN34, and TSEN2, which all encode tRNA splicing proteins . The study of mouse models will be essential to determine why developing cerebellar and pontine cells are particularly sensitive to the loss of these genes even though they are ubiquitously expressed.

Human studies have demonstrated that patient clinical phenotypes associated with severe congenital cerebellar malformations described here can be highly variable. Less severe cerebellar malformations have been reported in patients with non-syndromic MR , Autism Spectrum Disorders, and schizophrenia . Evidence of Purkinje cell dysfunction in cerebella from autistic patients has been demonstrated by reduced levels of glutamate decarboxylase (GAD67), which codes for a GABA-synthesizing enzyme . In addition, levels of various gene transcripts involved in GABAergic transmission are altered in lateral cerebellar hemispheres of schizophrenic patients. Specifically, GAD67, GAD65, GAT-1, MGLUR2, and NOS1 were downregulated whereas GABAA-alpha6, GABAA-delta, GLUR6, and GRIK5 were upregulated . Thus, it is likely that the genes underlying these more common and genetically complex neurodevelopmental disorders also influence cerebellar development. Notably, most patients with MR, autism, and other neurodevelopmental disorders rarely undergo brain imaging. Therefore, the coincidence of these disorders with cerebellar malformation is often missed. In order to fully and accurately delineate clinical phenotypes, we strongly advocate routine brain imaging of all human neurodevelopmental disorders. Further, given the extremely fine resolution with which cerebellar phenotypes can now be characterized in mice at the molecular, cellular, and systems level, mouse models for these common neurodevelopmental disorders are certain to be highly informative regarding their underlying pathology

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