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CEREBELLUM AND ITS CONNECTIONS

A REVIEW ON THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM THE GENETIC BASES OF ITS DISORDERS

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INTRODUCTION

The cerebellum is the region of the brain that is the latest to complete neurogenesis. In humans cerebellar development continues during the first year of life and in mouse for more than 2 weeks after birth. It arises from the dorsal aspect of the most anterior hindbrain called rhombomere1.

The study of cerebellar embryology begins with His' description of his Rautenlippe (rhombic lip) in a human embryo. In the fifth week the "dorsal rim (of the rhombencephalic alar plate) curves laterally and forms a fold which surrounds the entire rhombic cavity …". His divided the rhombencephalon and its rhombic lip, into rostral and caudal portions. The rostral (upper) rhombic lip will give rise to the cerebellum, the caudal (lower) rhombic lip to several precerebellar nuclei. The upper rhombic lip develops in two, bilateral swellings connected by a thin midline portion. At the midline, the cerebellum increases in bulk by the development of the cerebellar commissures and possibly by fusion of the intraventricular bulges. More recently the term "upper rhombic lip" is restricted to the posterior rim or germinal trigone of the cerebellar plate, with its attachment of the epithelial roof of the fourth ventricle, that should be distinguished from the ventricular zone, the neuroepithelium that covers its ventricular surface. The general opinion was that the cerebellum originates from the dorsal portion of the first

rhombomere. Several papers used the quail-chick marker system to trace the origin of the cerebellum. Substitution of the mesencephalic vesicle in chickens with a quail transplant resulted in the replacement of Purkinje cells and ependyma in the rostral cerebellum by cells with the typical massed quail chromatin in their nucleoli. According to Martinez and Alvarado-Mallart, these cells are present in a broad medial stripe, where labeled and non-labeled Purkinje cells occur together. Labeling is also found of the granule cells. According to Hallonet et al., the labeled Purkinje cells are found in a V-shaped, rostral region reaching caudally to lobule VIII. These authors denied the labeling of granule cells and concluded that these cells originate exclusively from the metencephalon, confirming the general opinion on this matter. Martinez and Alvarado-Mallart suggested that the rostral cerebellum might originate from the isthmic rhombomere, whereas its middle portion is a derivative of the first rhombomere. Its caudal portion, including the auricle and part of the avian lateral cerebellar nucleus, is derived from the second rhombomere. Sgaier et al. and Nieuwenhuys and Puelles pointed out that the cerebellar anlage rotates from an original rostrocaudal, to a medio-lateral position, due to the development of the pontine flexure. Purkinje cells produced by the ventricular zone maintain their medio-lateral position in the adult cerebellum. Those produced by the most medial (presumably isthmic rhombomere-derived) ventricular zone become located in the future vermis, subsequently more lateral parts of the ventricular zone give rise to Purkinje cells of more lateral parts of the hemisphere. Granule cells produced by the upper rhombic lip do not maintain their original medio-lateral position in the adult, due to their latero-medial tangential migration in the external granular layer (EGL).
Remarkably, the volume of the human cerebellum increases ~10× between 20 and 40 weeks of gestation, with the surface area increasing much more due to the formation of folia and lobules.

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.
The mouse cerebellum undergoes maximum growth and foliation after birth. Given the late development of the cerebellum compared to other brain regions, the cerebellum is particularly sensitive to environmental and clinical factors that impact on growth (or cause injury) around

birth. A better understanding of the factors that regulate progenitor cell expansion, production of neurons and glia, and their compartmentalization during foliation should pave the way for developing therapeutic approaches to stimulate endogenous progenitors to replenish cells lost due to injury. The developing cerebellum is unique among the brain regions as it has two zones that house neural stem and progenitor cells. Whereas in the rest of the central nervous system the ventricular zone (VZ) gives rise to all the neurons and glia, the VZ of the cerebellum is dedicated to making only inhibitory neurons (Purkinje cells and interneurons), as well as astrocyte-like glia (astrocytes and Bergmann glia referred to as astroglia). Interestingly, most of the interneurons and astroglia are generated from intermediate progenitors that leave the VZ and proliferate after birth in the cerebellar cortex. The second cerebellar progenitor zone is called the rhombic lip and generates the excitatory neurons of the cerebellum, primarily the granule cells, and projection neurons of the cerebellar nuclei. Like the astroglia and interneurons, the granule cells are generated from a secondary progenitor pool made up of granule cell precursors (GCPs) that are housed in the external granule cell layer (EGL) that covers the surface of the cerebellum during development and generates granule cells that migrate inward to form the internal granule cell layer (IGL). In humans, the EGL reaches a maximum volume after birth. It is tempting to speculate that a dedicated transient amplifying progenitor pool evolved for the granule cells, because the granule cells comprise a majority of the neurons in the brain and thus require massive expansion of progenitor numbers during development. Curiously, the source of most oligodendrocytes for the cerebellum appears to be the VZ outside the cerebellum, likely the midbrain and/or ventral rhombomere1.

THE 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.

TYPES OF HUMAN CEREBELLAR MALFORMATIONS

The role of the cerebellum is more than just motor activity. Because of the widespread connections between the cerebellum and other brain areas, the cerebellum has been considered to be a part of the brain that has a main role in emotion, cognition, behavior, and social interactions. Thus, any damage to the cerebellum early in development could have a deep impact on movement, cognition, and learning. Autism and ADHD are well-known developmental disorders of the cerebellum. Others include: Williams syndrome, schizophrenia, medulloblastoma and cerebellar ataxia. There are some other disorders of the cerebellum such as the Joubert syndrome and related disorders (JSRD), Dandy–Walker malformation (DWM), pontocerebellar hypoplasia (PCH), cerebellar vermis hypoplasia (CVH), and developmental dyslexia that occur during development, but so far, there is no data available about any association of neurotrophic factors with these conditions, which suggests new areas of research. Neurotrophic factors modulate formation of the central nervous system by affecting the development and differentiation of neuronal cells in utero. The neurotrophin family of peptides was the first discovered family of growth factors that affect the central nervous system. These proteins are also expressed throughout life and have central roles in the regulation of action and survival of neurons and glial cells. Receptors for these factors have also been discovered in many tissues where they mediate a wide range of actions including the morphogenesis of kidney and differentiation of vessels and immune cells. Neurons and glial cells are dependent on growth factors for their normal function, differentiation, and survival. Neurotrophic factors are classified into three groups: neurotrophins (NTs), the transforming growth factor-beta (TGF-β) superfamily, and neurotrophic cytokines.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Dysfunction of the cerebellum is a characteristic of some developmental disorders such as ADHD. Studies implicate frontostriatal and frontocerebellar catecholaminergic circuit disorders in ADH pathophysiology. Because antidepressants and psychostimulants used to treat patients with ADHD increase BDNF levels, it proposed that this neurotrophic factor plays an important role in the pathogenesis of ADHD. Many studies on the pathogenesis of ADHD have focused on and confirmed the genetic association of the BDNF gene or its polymorphisms with ADHD. A recent large-scale DNA sequencing study supported this association. The BDNF Val66Met polymorphism has been studied the most, but its association with ADHD is questionable. Park et al. showed a significant interaction between the neurotic symptoms of ADHA and the BDNF met allele in a Korean population. However, a meta-analysis conducted on four European populations refuted the involvement of BDNF Val66Met polymorphism with pathogenesis of ADHD. Recently, another study was performed to address this controversy. Other investigators focused on the levels of neurotrophic factors in the blood, especially BDNF and its role in the pathogenesis of ADHD. The plasma level of BDNF in 41 drug-naive child ADHD patients was higher than that in 107 healthy controls. A later study by the same group confirmed these findings, while Scassellati et al. showed no difference in the serum BDNF level between healthy and affected groups using the same samples. A study enrolling Caucasian adult ADHD patients showed that these patients had decreased serum NT levels compared with the control group. The role of NGF and its receptor (NGFR) has been shown in ADHD. NGF exerts a trophic and functional role in the basal forebrain cholinergic neurons, which are involved in attention. Serum NGF levels were higher in drug-naive ADHD patients at childhood. Bilgic et al. showed that

serum NGF and BDNF levels in Turkish children were not significantly associated with ADHD, while serum GDNF and NT3 were higher in the patient group; however, they suggested that the NT serum level was not associated with severity of ADHD.

AUTISM SPECTRUM DISORDERS

Autism spectrum disorders (ASDs) are neurodevelopmental disorders that impairs communication and social ability. Both genetic and environmental factors are involved in etiology of ASD, and cerebellar involvement in ASD has been recognized (see chapter "Neurodevelopmental Disorders of the Cerebellum: Autism Spectrum Disorder"). In some animal models of ASD including Borna disease virus infection and rats treated with valproic acid, a gradual loss of Purkinje cells diminishes cerebellum size and induces other aspects of cognitive deficits. Measurement of neurotrophin mRNA levels such as NGF, BDNF, and NT-3 and their respective TRK receptors in newborn rats infected with Borna disease virus showed that there were no alterations in the cerebellum. However, there were an increased number of apoptotic cells in the cerebellar granular layer and loss of cerebellar Purkinje cells. A study on blood spot from newborns who were later diagnosed with ASD showed decreased NT-3 and NT4/5 levels compared with healthy subjects. Similarly, in a postmortem study, the cerebellar NT-3 level was higher in ASD patient than in normal controls. Another neurodevelopmental rodent model that mimics prenatal immune activation as an environmental risk factors for ASD and schizophrenia is the maternal lipopolysaccharide (LPS) exposure rat model. LPS-treated pups on P21 show increased levels of cerebellar NT-3. Levels of neurotrophins are increased in the blood of children with ASD. The elevated levels of the serum NGF and other neurotrophins can be associated with the development of ASD and mental retardation later in childhood. A variant type of BDNF has been found in autistic families in addition to increased blood levels of this neurotrophin in ASD children. Therefore, BDNF has been proposed as a critical factor that is involved in ASD and is a therapeutic targeted that is being studied. Conversely, another review proposed a decreased blood level of BDNF as a marker for ASD prediction and prognosis. Sadakata et al. reported that transgenic knockout mice that are missing Ca2+dependent activator protein for secretion 2 (CAPS2), a protein that is involved in NT release, were susceptible to autistic features. Nickl-Jockschat et al. discussed that altered neurotrophin levels are a pathological mechanism. As mentioned earlier, there is more affinity of pro-NT to activate p75NTR and subsequently more apoptotic cell death, and therefore the changes in the ratio of pro-NT to NT can result in some pathological aspects. Neurotrophins such as NGF and BDNF play a role in dendritic morphology. Dendritic shape abnormalities and a larger amount of dendritic spines have been detected in ASD patients. The cerebellum and inferior olive size variations have been reported in postmortem examinations of brains from ASD patients. These anomalies in dendritic branching happened in other neurodevelopmental disorders linked to ASD, such as Fragile X and Rett syndrome (RTT). RTT is a genetic disorder that is considered to be an ASD (see chapter "Epigenetics and Cerebellar Neurodevelopmental Disorders"). However, for years there was a debate on the classification of RTT as an autistic developmental disorder, and in 2013, the American Society of Psychiatry changed the classification of RTT and removed it from the ASDs because of its unique molecular basis. RTT affects girls, and mutations in the X-linked gene encoding methyl–CpG- binding protein 2 (MeCP2) are responsible for over 80%

of affected girls. MeCP2 alters the expression of many genes in the cerebellum. While serum BDNF levels in RTT girls and in a normal group are similar, BDNF protein levels are reduced in RTT brains. Reduced or unaltered NGF in the cerebellum and other brain regions has been reported. Calamandri et al. showed that serum NGF levels decreased with age.

ATAXIA

Cerebellar ataxias are neurological disorders that can affect vermis, paravermis, and hemisphere of the cerebellum during development (see chapter "Motor Circuit Abnormalities During Cerebellar Development"). Machado–Joseph disease (MJD) or spinocerebellar ataxia type 3 (SCA3) is a hereditary ataxia that is caused by repeated CAG in the ATXN3 gene. Neuronal loss in the cerebellar nuclei and Purkinje cell layer has been reported in MJD. Since p75NTR has an important role in the induction of neuronal apoptosis, these findings encouraged researchers to investigate the role of p75NTR in the naked-ataxia mutant mouse, but p75NTR expression showed a normal pattern in this type of ataxia. Because NGF and its receptor TkrA exist in human cerebellar neurons and are involved in cerebellar development and stability of the cerebellar connections, NGF therapy may improve symptoms in patients with SCA3. Jones et al. showed that mesenchymal stem cells improve survival of Purkinje cells by expression of BDNF, NT-3, or GDNF. Detection of neurotrophin mRNA expression in the ataxic stargazer mutant mouse showed that NT-3 or NGF mRNA expression in the cerebellum was normal while BDNF mRNA in the cerebellar granule cell layer was reduced. In the SCA6, decreased BDNF mRNA expression and altered BDNF protein levels in Purkinje cell dendrites have been shown.

MEDULLOBLASTOMA

Medulloblastoma is the most common pediatric brain tumor in the cerebellum of infants and children (see chapters "Primary Pediatric Brain Tumors of the Posterior Fossa and Primary Pediatric Brain Tumors of the Posterior Fossa"). Marchetti et al. suggested a critical role for NTs and their receptors in the invasive feature of human medulloblastoma. Although as previously mentioned, Trks are important factors for neuronal survival, but NGF/TrkA signal transduction is accompanied by suppression of medulloblastoma cell proliferation and induction of cell death. Interaction of the cytoplasmic adaptor protein CCM2 with the TrkA receptor is necessary in this pathway. The mediator of TrkA-CCM2 death signaling in medulloblastoma cells is STK25, which is a germinal center kinase class III (GCKIII) kinase (STK24, STK25). Reduction of STK25 prevents medulloblastoma cell death induced by NGF-TrkA. Another study involving a cellular model of medulloblastoma reported induction of cell death after activation of TrkA by NGF through macropinocytosis. Valderrama et al.'s findings confirmed that induction of TrkA expression resulted in either medulloblastoma cell differentiation or apoptosis. Whole genome microarray analysis revealed that TGFβ is a potent factor that influences progression and metastasis of tumor cells in. Gate et al. showed that obstruction of TGFβ signaling almost completely eliminates T regulatory cells and improves CD8(+)/killer cell function to eradicate tumor cells.

SCHIZOPHRENIA

Schizophrenia, which is classified as a late-onset neurodevelopmental disorder, is a hereditary (80%) chronic mental disease with cognitive abnormalities. Involvement of cortico-cerebellar connections in cognition has been suggested by brain imaging studies. Researchers have suggested that schizophrenia may be related to cerebellar anomalies including a size and density decrease of Purkinje cells and remodeling of synaptic protein expression in the cerebellum. There is growing evidence of a role for neurotrophin in the pathophysiology of schizophrenia. Some studies showed the difference in plasma BDNF and NGF levels between schizophrenic patients and normal people. The levels of NGF in schizophrenia have been reported to be lower than in normal people, while there were no differences in BDNF or NGF levels in peripheral blood mononuclear cells (PBMCs) in patients and controls in the Martinez study. However, Paz et al. reported increased BDNF levels in the cerebellar cortex of schizophernic patients. In newly diagnosed psychosis patients, serum NGF levels decrease, and this may be a good biomarker in the diagnosis or screening for patients with schizophrenia. A synaptic plasticity defect observed in schizophrenia may be associated with NGF and its receptor (NGFR). A positive association between schizophrenia and both the NGF rs6330 and the NGFR rs11466155 and rs2072446 SNPs was reported. Alterations of neurotrophins in an animal model of schizophrenia have been confirmed. In animals injected subchronically with ketamine (Ket), which is a good model to study schizophrenia, Becker et al. reported that NGF, NT-3, and BDNF mRNA levels and their tyrosine kinase receptors changed in several brain regions and in the cerebellum. A decrease in NGF levels in drug abusers was also reported. The role of neurotrophin in schizophrenia suggests that reduced levels of neurotrophins may increase the risk of psychosis in drug users.

WILLIAMS SYNDROME

Williams syndrome (WS) is a rare neurodevelopmental disorder that affects 2–5/100,000 people, and it is caused by a 1.6 Mb deletion on chromosome 7. This syndrome is characterized by an enlarged cerebellum and mild- to- moderate mental retardation with a deficit in visuospatial processing and an oversensitivity to sound. NGF levels in the serum of WS patients are higher than in normal people, and they remain continuously higher during childhood. This is on contrast to normal people, who have a higher serum NGF only in early childhood.

DANDY–WALKER MALFORMATION (DWM) AND CEREBELLAR VERMIS HYPOPLASIA (CVH)

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. 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.

JOUBERT SYNDROME AND RELATED DISORDERS (JSRD)

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. 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 provides 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.

PONTOCEREBELLAR HYPOPLASIA (PCH)

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. 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.

CONCLUSION

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, routine brain imaging of all human neurodevelopmental disorders is advised. 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.

REFERENCES

- Novel Approaches to Studying the Genetic Basis of Cerebellar Development by Samin A. Sajan,, Kathryn E. Waimey, and Kathleen J. Millen

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/

- Contemporary Clinical Neuroscience Development of the Cerebellum from Molecular Aspects to Diseases (Editor- Hassan Marzban)

  - Cellular and Genetic Programs Underlying Cerebellum Development by Alexandra L. Joyner, Ryan Willett, and Andrew Lawton
  - Developmental Disorders of the Cerebellum and Neurotrophic Factors by Leila Pirmoradi, Ali Akbar Owji, and Shahla Shojaei