**A review on the developmental genetics of cerebellum and the genetic basis of known cerebellar disorders**

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**DEVELOPMENTAL GENETICS OF CEREBELLUM**

The developmental mechanisms that coordinate the establishment of cerebellar structure and circuitry provide a powerful model for understanding how functional brain networks are formed. Two primary germinal zones generate the cells that make up the cerebellum. Each zone expresses a specific set of genes that establish the cell lineages within the cerebellar anlage. Then, cohorts of differentiated projection neurons and interneuron progenitors migrate into the developing cerebellum. Thereafter, a number of remarkable patterning events occur including transformation of the smooth cerebellar surface into an intricately patterned series of folds, formation of three distinct cellular layers, and the demarcation of parasagittal gene expression domains. Together, these structural and molecular organizations are thought to support the proper connectivity between incoming afferent projections and their target cells. After birth, genetic programs and neural activity re-pattern synaptic connections into topographic neural networks called modules, which are organized around a longitudinal zone plan and are defined by their molecular, anatomic, and functional properties.

During embryonic development, Purkinje cells in the cerebellum and neurons in the inferior olive follow a simultaneous, but independent, process of intrinsic parcellation, giving rise to subsets of biochemically different cortical compartments. The occurrence of positional information shared between olivary axons and their postsynaptic targets, the Purkinje cells, provides a molecular code for the formation of coarse-grained maps. Activity-dependent mechanisms are required for the transition from crude to fine-grained maps. This important refinement, which confers ultimate specificity to the maps, is under the regulation of parallel fiber-Purkinje cell synaptic activity.

The cerebellum represents 10% of the brain's total volume, but contains more than half of our neurons. It acts as a coordination centre, using sensory inputs from the periphery to fine-tune our movement and balance. It is one of the first structures in the brain to begin to differentiate, but one of the last to mature, and its cellular organization continues to change for many months after birth. The study of mouse homologues of *Drosophila* genes has provided valuable insights into the molecular basis of cerebellar development.

In humans, the cerebellum develops from the dorsal region of the posterior neural tube, and its cells arise from two germinal matrices. Most cells are derived from the ventricular zone, but the granule neurons come from a specialized germinal matrix called the rhombic lip.

The mesencephalon and metencephalon both contribute to the developing mouse cerebellum. The patterning of these two regions depends on signals from the isthmus organizer (IO), located just caudal to their junction. *Otx2* and *Gbx2* are central to IO development. *Otx2* is expressed in the mesencephalon, with a posterior boundary at the rostral metencephalon; *Gbx2* is expressed in the metencephalon, and its anterior boundary abuts the *Otx2* boundary. Reciprocal repression maintains a sharp boundary between these domains. *Otx2* and *Gbx2* form part of a regulatory loop that includes *Wnt1*, *En1* and *Fgf8*. Many other genes, including members of the Pax and Hox families, are also involved in patterning this region.

Purkinje cells (PCs), Golgi neurons, stellate and basket cells all arise from the ventricular neuroepithelium. PCs are born around embryonic day 13, and they migrate along radial glial fibres into the cerebellar anlage. During their final maturation phase, PCs develop extensive dendritic arbors and synapse onto granule neurons. This depends on granule neuron signals, probably including *Wnt3*. Various growth factors are required for PC survival, including nerve growth factor, acetylcholine, neurotrophin 4/5, brain-derived neurotrophic factor and ciliary neurotrophic factor.

The rhombic lip, located between the fourth ventricle and the metencephalic roof plate, gives rise to granule neurons. Proliferation in its germinal epithelium is governed by the *Math1* gene. Rhombic lip cells migrate to the cerebellar anlage and settle on its periphery to form the external granule layer, another zone of proliferation. As the cells begin to migrate, they express markers that include *RU49/Zipro1*, *Zic1* and *Zic3*. *RU49/Zipro1* and *Zic1* are thought to be involved in cell proliferation, which requires interaction with PCs. PCs might release a diffusible factor such as sonic hedgehog (Shh), and *Zic1* could control cell proliferation by indirectly regulating the S*hh* pathway. The final stage of granule neuron maturation occurs after precursor cell migration into the inner granule layer.

Many genes, including *En1*, *En2*, *Pax2*, *Wnt7b*, and some of the ephrins and their receptors, show characteristic patterns of spatial expression in the cerebellum, but only *En2* has been studied specifically for its role in compartmentalization. In addition to the patterning genes, several other gene families, such as the heat shock proteins and proteins involved in neuronal migration, are also expressed in specific patterns. Spatial- and temporal-specific knockout strategies should yield more information about the roles of these genes in patterning the cerebellum.

Although it is easiest to consider how developmental phases fit together in the mammal, it is important to recognise that, beyond the stereotyped neuronal Purkinje-granule cell circuit, evolutionary variability in cerebellum form reflects variability in how these phases are deployed in the embryo. Thus, the territory that will generate the cerebellum – its ‘anlage’ – is allocated during the early embryonic segmental phase of hindbrain development close to the boundary (the ‘isthmus’) between the hindbrain and the midbrain. However, regulation of patterning in this earliest phase seems particularly important for the development of the uniquely mammalian midline expanded region of the cerebellum known as the ‘vermis’.

Lagging behind the establishment of rhombomere boundaries, specific cell types are allocated along the dorsoventral axis. For glutamatergic cells of the cerebellum, this is a remarkably prolonged and, importantly, a dynamic process that takes place at the most dorsal interface between neural and non-neural ‘roof plate’ tissue: the rhombic lip. This phase generates the basic dichotomy between GABAergic and glutamatergic cell types that underlies the conserved Purkinje-granule cell circuit, but it is also responsible for the diversity of cerebellum output connectivity across species.

Cell type allocation precedes a third, distinct temporal phase of development that extends into early prenatal life (up to 2 years in humans). Here, the principal derivative of the rhombic lip, the granule cell precursor, accumulates over the surface of the cerebellum and undergoes further rounds of symmetric divisions in a process of transit amplification that exponentially expands its numbers. Growing evidence suggests that this most investigated phase of cerebellum development is substantially reduced or absent in aquatic vertebrates.The final form of the mammalian cerebellum is so much a product of the first and third phases of development.

**GENETIC BASIS OF KNOWN CEREBELLAR DISORDERS**

The list of genes that when mutated cause disruptions in cerebellar development is rapidly increasing.  Improvements in brain imaging, such as magnetic resonance imaging (MRI) and the emergence of better classification schemes for human cerebellar malformations, have recently led to the identification of a number of genes which cause human cerebellar disorders. Combining classical molecular techniques, genomics, and mouse models of human malformations will be essential to fuel additional discoveries of cerebellar developmental genes and mechanisms.

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. 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.

**Dandy–Walker malformation (DWM)**

Within the broad spectrum of dysgenetic abnormalities in the posterior fossa, the most common lesions involve

impaired vermis development associated with increased cerebrospinal-fluid spaces. There is ongoing controversy as to whether these developmental anomalies are separate entities or part of a continuum. The most striking of these anomalies is Dandy–Walker malformation (DWM), in which the enlarged cerebrospinalfluid space results from cystic distention of the fourth ventricle, with complete or partial agenesis of the cerebellar vermis, hypoplasia of the cerebellar hemispheres, and enlargement of the posterior fossa with

elevation of the torcula and anterior displacement of the brainstem; hydrocephalus develops in most cases. The pathogenetic mechanism(s) leading to the DWM remain poorly understood. How much of the morphological picture is primary dysgenesis, and how much is secondary distortion/restriction of cerebellar growth and development by the often massively distended fourth ventricular cyst, remains unclear. In one view the cyst develops after failed incorporation of the anterior membranous area into the choroid plexus and failed or delayed development of the foramen of Magendie in the posterior membranous area. Of note, at autopsy many cases of DWM appear to have patent fourthventricular foramina.

An anomaly at the opposite end of this spectrum is isolated inferior vermian hypoplasia with normal cerebellar hemispheres and brainstem. This lesion appears to represent an arrested incomplete downgrowth of the vermis, leaving an enlarged midline cerebrospinal fluid space which may be mistaken for a cystic lesion. Advances in magnetic resonance imaging (MRI) have increased the detection of more subtle forms of inferior vermian hypoplasia. The possibility of over-diagnosis of this lesion was emphasized by Limperopoulos et al,

who showed that 32% of isolated inferior vermian hypoplasia cases diagnosed by fetal MRI in the second trimester were normal by postnatal MRI.

This study raised important questions about both the sensitivity and specificity of fetal MRI, as well as possible normal variations in the time course of vermian development. The diagnostic entity of isolated inferior vermian hypoplasia continues to be inconsistently used. For example, some authors consider this lesion a normal variant, while others refer to it as the Dandy–Walker variant despite the fact that it lacks a cystic fourth ventricle and has a normal-sized posterior fossa. It is increasingly advocated that the term Dandy–Walker variant be abandoned altogether given its multiple and variable definitions, lack of specificity, and ongoing confusion with the true DWM. Finally, available evidence regarding the outcome of children with isolated inferior vermian hypoplasia is conflicting, with recent studies suggesting a far more favorable outcome than that reported earlier.

**Pontocerebellar hypoplasia (PCH)**

Development of the cerebellum and brainstem are intimately connected. For example, the rhombic lips generate cells that lead to formation of the external granular layer of the cerebellum as well as cells to the pontine and precerebellar nuclei, such as the inferior olive. It is therefore not surprising that malformations of the cerebellum and brainstem often occur together. Joubert syndrome is an autosomal recessive condition that presents with hypotonia, disturbances in respiratory (hyperventilation and central apnea) and oculomotor control, and later psychomotor disturbances. The essential brain morphology of Joubert syndrome includes vermian hypoplasia, impaired axonal decussation (with a deep interpeduncular notch), and thick abnormally oriented superior cerebellar peduncles. Together these features give the neuroradiologic picture known as the molar tooth sign. Previously thought to be pathognomonic for Joubert syndrome, the molar tooth sign is now recognized in at least eight other conditions, known as Joubert syndrome-related disorders, often with cerebral, renal, retinal, or hepatic abnormalities. At least four genetic loci have been identified for Joubert syndrome, including mutations in the AHI1 and NPHP1 genes. The gene product of AHI1 (Jouberin) guides axonal decussation of the corticospinal tracts and superior cerebellar peduncles, both of which are disturbed in Joubert syndrome and Joubert syndromerelated disorders.

Pontocerebellar hypoplasia (PCH) is a heterogeneous group of conditions having in common an abnormally small cerebellum and pons. When the inferior olives are also involved, the term olivopontocerebellar hypoplasia is used. The pathogenetic mechanisms underlying these conditions remain unclear although both hypoplasia and atrophy (and their combination) have been implicated. To date, five forms of PCH have been described, distinguished by the presence of associated clinical and pathological findings. Thus, in addition to a small cerebellum and pons, PCH-1 has anterior horn-cell degeneration with spinal muscular atrophy, while PCH-2 has prominent extrapyramidal dyskinesias and progressive microcephaly. These two original forms of PCH described by Barth are distinguished from other forms of PCH by relative preservation of the vermis. PCH-3 is associated with optic atrophy, progressive microcephaly, and severe congenital hypotonia, whereas PCH-4 is distinguished by relatively preserved cerebellar foliation patterns. The most recently described PCH-5 form is a severe condition with a hypocellular vermis and fetal-onset myoclonic seizure-like activity.

The combination of cerebellar and pontine hypoplasia suggests a rhombic-lip defect. Since the Math1 gene is heavily expressed in the rhombic lips, and since a knockout mouse model develops neither the external granular layer nor the pontine nuclei, this gene locus has been implicated in this group of disorders. Many cases appear to have a genetic origin, with an autosomal recessive inheritance pattern. Although the precise gene loci for PCH are largely unknown, linkage studies in a recently described form of PCH (with associated progressive microcephaly, seizures, and developmental delay) have identified a genetic locus on chromosome. Certain inborn errors of metabolism may manifest with combined cerebellar-brainstem malformation and atrophy, including congenital disorder of glycosylation type Ia and the Smith–Lemli–Opitz syndrome.

**Joubert syndrome**

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**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.

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.

### Types of Human Cerebellar Malformations

Advances in imaging, genetics, and classification are enabling previously consolidated malformations to be delineated into distinct categories. 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.

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Fig.1

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

|  |  |  |
| --- | --- | --- |
| Cerebellar malformations | Implicated human genes | Likely disrupted process |
| Cerebellar vermis hypoplasia (CVH) | OPHN1 | Spine morphogenesis |
| Dandy–Walker malformation (DWM) | ZIC1, ZIC4, FOXC1 | Granule cell differentiation |
| Joubert syndrome and related disorders (JSRD) | AHI1, ARL13B, CCD2A, CEP290, INPP5E, NPHP1, RPGRIP1L, and TMEM67 | Granule cell proliferation |
| Pontocerebellar hypoplasia (PCH) | CASK, RARS2, TSEN54, TSEN34, and TSEN2 | 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, there should be 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.

**ATAXIA**

The hereditary ataxias are a very heterogeneous group of disorders characterized by cerebellar dysfunction that can be either isolated or accompanied by other neurological manifestations. The classification of the hereditary ataxias based on clinical or histopathological findings has been difficult because of the significant overlap of phenotypes among the various genotypes. The patterns of inheritance observed in ataxias include autosomal dominant, autosomal recessive and X-linked. Friedreich's ataxia, the most frequent form among the recessive ataxias, has been mapped to the long arm of chromosome 9 based on close linkage to the markers D9S5 and D9S15. This close linkage allows the use of these two DNA markers for prenatal diagnosis in families with one affected offspring. In the past year, significant research progress has been accomplished by applying molecular genetic studies to the dominantly inherited spinocerebellar ataxias. Spinocerebellar ataxia type 1 (SCA1), which maps to the short arm of chromosome 6, has been found to be caused by expansion of an unstable trinucleotide (CAG) repeat. This mutational mechanism explains the presence of the clinical phenomenon of anticipation in some families with SCA1. The finding of an unstable repeat in SCA1 will facilitate the diagnosis of SCA1 in familial and isolated cases and will allow preclinical and prenatal diagnosis in families with this disease. In addition to the cloning of the SCA1 gene, two dominantly inherited ataxias have been genetically mapped: SCA2, to the long arm of chromosome 12, and Machado-Joseph disease (MJD), to the long arm of chromosome 14. Given that anticipation has been observed in patients with SCA2 and MJD, it is likely that trinucleotide repeat expansion could be a common mechanism involved in all the spinocerebellar ataxias. Last, significant research progress has been accomplished in the field of hereditary ataxias associated with DNA repair defects which should facilitate our understanding of mechanisms involved in cerebellar degeneration.

**NYSTAGMUS**

Infantile Nystagmus (IN) displays extreme genetic and clinical heterogeneity, and the most common form of IN follows an X-linked pattern. X-linked infantile nystagmus is associated with mutations of the gene [FRMD7](https://en.wikipedia.org/wiki/FRMD7), which is located on the [X chromosome](https://en.wikipedia.org/wiki/X_chromosome). To date, two major genes, FRMD7 and GPR143, have been identified as the causative genes of hereditary X-linked infantile nystagmus (XLIN).The FRMD7 gene contains an N-terminal FERM (F for 4.1 protein, E for ezrin, R for radixin and M for moesin) highly conserved domain and a FERM-adjacent domain without significant homology. Mutations in the FRMD7 gene are currently thought to be the most common cause of XLIN.Gene expression occurs mainly in the retina and in those parts of the brain that coordinate eye movement, like the cerebellum and the lateral ventricles.  Although the exact function of this gene is still unclear, previous research showed that FRMD7 gene mutations may lead to nystagmus by disrupting the normal development of certain nerve cells in the brain and the retina. Most studies focused on the N-terminal FERM domain which may link the plasma membrane and the actin cytoskeleton. Previous studies also suggested a link between membrane extension during neuronal development and remodelling of the actin cytoskeleton. The other gene causing XLIN, GPR143, encodes a protein that binds to heterotrimeric G proteins and affects pigment production in the iris, retinal pigment epithelium and skin. This protein is thought to be involved in intracellular signal transduction. Mutations in GPR143 have also been shown to cause X-linked ocular albinism type 1 (OA1), which is a multi-symptom syndrome that can cause reduced visual acuity, nystagmus and strabismus.However, a deletion mutation of the GPR143 gene has also been reported in a Chinese IN family without the typical phenotype of ocular albinism.Nearly half of X-linked IN families have genetic defects in the FRMD7 gene. However, very few studies have investigated the genetic basis of sporadic cases of IN.

**CEREBELLAR AGENESIS**

The etiology of cerebellar agenesis is not uniform, but varied (heterogeneous). Acquired (prenatal/perinatal) causes include cerebellar destruction caused by hemorrhage, lack of or diminished blood flow (ischemia), or other factors. This has been documented in a minority of children with spina bifida (myelomeningocele), also called “vanishing cerebellum in myelomeningocele”. It is being increasingly recognized in premature babies with very low birth weight (also called “cerebellar disruption of prematurity”), and is often accompanied by additional anomalies of the brain.

The exact cause of isolated cerebellar agenesis often remains unknown. Most cases occur randomly for unknown reasons (sporadically). A genetic cause is only documented in an extremely rare syndrome of cerebellar agenesis and agenesis of the pancreas, resulting in neonatal diabetes mellitus. This syndrome is caused by mutations in the PTF1A gene, and it is inherited in an autosomal recessive manner.

**HYPOTONIA**

Hypotonia can be caused by conditions that affect the brain, [central nervous system](https://www.healthline.com/human-body-maps/nervous-system#2), or muscles. These conditions include:

* [cerebral palsy](https://www.healthline.com/health/cerebral-palsy)
* [brain damage](https://www.healthline.com/health/brain-damage), which can be caused by lack of oxygen at birth
* [muscular dystrophy](https://www.healthline.com/health/muscular-dystrophy)

In many cases, these chronic conditions require lifelong care and treatment. Hypotonia can also be caused by genetic conditions. These conditions include:

* [Down syndrome](https://www.healthline.com/health/down-syndrome)
* Prader-Willi syndrome
* [Tay-Sachs disease](https://www.healthline.com/health/tay-sachs-disease)
* [trisomy 13](https://www.healthline.com/health/triploidy)

Children with Down syndrome and Prader-Willi syndrome often benefit from therapy. Children with Tay-Sachs disease and trisomy 13 typically have shortened lives. Rarely, hypotonia is caused by [botulism infections](https://www.healthline.com/health/botulism) or contact with poisons or toxins. However, the hypotonia often goes away after you recover.

**DYSDIACOCHOKINESIA(DDK)**

DDK most often comes from a disturbance in the cerebellum. The cerebellum is a large part of the brain that controls voluntary muscle movements, posture, and balance. It’s thought that people with DDK are unable to switch opposing muscle groups on and off in a coordinated manner.

DDK may be the result of an underlying cerebral condition, such as:

* multiple sclerosis
* [Friedreich’s ataxia](https://www.healthline.com/health/friedreichs-ataxia)
* ataxic dysarthria (a speech disorder)

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