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**CEREBELLUM AND ITS CONNECTIONS**

**Question**

Write a concise review on the developmental genetics of the cerebellum and highlight the genetic bases of known cerebellar disorders.

**Answer**

The cerebellum is a pivotal centre for the integration and processing of motor and sensory information. Over time, various approaches have been made to the contribution of the understanding of the mature cerebellum. 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 and this makes it suitable for genetic studies.

Disruption of human cerebellar development is often severely handicapping but not lethal, making it suitable for genetic analysis. Human cerebellar malformations have been used to identify cerebellar developmental genes. Recent genetic lineage and loss-of-function data from mice have revealed unique and non-overlapping anatomical origins for GABAergic neurons from ventricular zone precursors and glutamatergic cell from rhombic lip precursors, mirroring distinct origins for these neurotransmitter-specific cell types in the cerebral cortex. Mouse studies elucidating the role of Ptf1a as a cerebellar ventricular zone GABAergic fate switch were actually preceded by the recognition that PTF1A mutations in humans cause cerebellar agenesis, a birth defect of the human cerebellum. Indeed, several genes for congenital human cerebellar malformations have recently been identified, including genes causing Joubert syndrome, Dandy-Walker malformation and Ponto-cerebellar hypoplasia.

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

GENES INVOLVED IN VARIOUS STAGES OF CEREBLLAR DEVELOPMENT

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| --- | --- | --- |
| S/N | STAGES/AREAS OF DEVELOPMENT | GENES, PROTEINS AND MOLECULES |
| 1 | Cerebellar primordium | Otx2, Gbx2, Fgf8, Wnt1, En1/2, Pax2/5, Bmps, Shh, Hoxa2 |
| 2 | Granule cell generation | Math1, RU49/Zipro1, Zic1,2,3, Shh pathway, Ccnd2, p27, Neurod1, NSCL1 |
| 3 | Granule cell migration | Tag1, Tuj1, Pax6, Dcc/netrin pathway, Unc5h2,3 GIRK2, astrotactin, thrombospondin, tenascin, neuregulin |
| 4 | Purkinje cell maintenance | Ngf, BDNF, ciliary neurotrophic factor, acetylcholine, Nt4/5, Rorα |
| 5 | Purkinje cell migration | Reelin pathway |

The neural tube can be thought of as comprising four different regions during early development. The most anterior portion of the neural tube, the prosencephalon, gives rise to the forebrain. The mesencephalon, just caudal to the prosencephalon, gives rise to the midbrain, whereas hindbrain regions evolve from the metencephalon and myelencephalon.

The proper patterning of the mesencephalon and the metencephalon is dependent on molecular signals released from the ISTHMUS organizer (IO), which is located just caudal to the junction of these two regions. Morphologically, this region is marked by a sharp bend of the neural tube. It has been shown in various mouse mutants, as well as in transplant experiments, that the IO is necessary and sufficient for patterning the mid-/ hindbrain region from the neural tube. The IO is, in turn, set up by the expression of a complex array of genes. Two, in particular, are central to its development: Otx2, one of the mouse homologues of the Drosophila gene orthodenticle, and Gbx2, a homologue of the Drosophila gene unplugged. At embryonic day, Otx2 is expressed in the mesencephalon, with a posterior boundary at the rostral metencephalon, whereas Gbx2 expression in the metencephalon is bounded anteriorly by the caudal mesencephalon.

The sharp boundary between the expression domains of these two genes reflects their reciprocal repression. In addition to helping form the IO molecularly, Gbx2 and Otx2 also regulate the expression of Fgf8 (fibroblast growth factor 8); Otx2 negatively regulates Fgf8expression, whereas Gbx2 maintains its.Fgf8is involved in regulating the various genes expressed in the mid- and hindbrain regions.

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

 In the absence of Ptf1a, cerebellar VZ fails to generate all of the known GABAergic cerebellar neuronal subtypes including Purkinje cells (PCs), stellate and basket cells and a subset of deep cerebellar neurons, which constitute the main outflow tract of the cerebellum. Fate mapping of Ptf1a+ cells in wild-type mice demonstrates that Ptf1a+ VZ cells are normally fated to produce all of these GABAergic cerebellar cell types and thus, their loss is caused by a primary failure of the VZ to produce appropriate neurons in the absence of Ptf1a.

It is known that cerebellar RL expressing Math1 is the source of all cerebellar granule neurons. Recent genetic fate mapping of Math1+ cells, combined with newly developed cerebellar slice culture assays have completely revolutionized our understanding of the cerebellar RL. Surprisingly, the Math1+ RL gives rise not only to glutamatergic granule neurons, but to all known glutamatergic neurons of the cerebellum. These include both unipolar brush cells, which serve as a relay cell amplifying the excitatory effects of mossy afferent fibers on granule cells, as well as the glutamateric subset of deep cerebellar nuclei neurons. Thus, the well ordered cellular organization of the mature cerebellum is achieved through the bipartite origins of its constituent neurons. Despite the complexity of the final mature structure, the cerebellum is not that different from the developing spinal cord and telencephalon, where distinctly ordered progenitors along the dorsal/ventral axis of the neural tube give rise to cells of distinct neurotransmitter phenotypes.

Recent studies have determined that both RL induction and Math1 expression is dependent on Bmp-derived signals from the adjacent roof plate. Further, the roof plate Bmp signal is countered by antagonistic Notch1 activity within the cerebellar ventricular zone. Thus, antagonism between the Notch and BMP signaling pathways regulates the differentiation of cerebellar progenitors throughout the period of cerebellar neurogenesis.

**The following disorders listed below are examples of cerebellar disorders:**

* **Huntington disease:**

Huntington disease is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition). Adult-onset Huntington disease, the most common form of this disorder, usually appears in a person's thirties or forties. Early signs and symptoms can include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions. Many people with Huntington disease develop involuntary jerking or twitching movements known as chorea. As the disease progresses, these movements become more pronounced. Affected individuals may have trouble walking, speaking, and swallowing.

People with this disorder also experience changes in personality and a decline in thinking and reasoning abilities. Individuals with the adult-onset form of Huntington disease usually live about 15 to 20 years after signs and symptoms begin. A less common form of Huntington disease known as the juvenile form begins in childhood or adolescence. It also involves movement problems and mental and emotional changes. Additional signs of the juvenile form include slow movements, clumsiness, frequent falling, rigidity, slurred speech, and drooling. School performance declines as thinking and reasoning abilities become impaired. Seizures occur in 30 percent to 50 percent of children with this condition. Juvenile Huntington disease tends to progress more quickly than the adult onset form; affected individuals usually live

10 to 15 years after signs and symptoms appear.

Mutations in the HTT gene cause Huntington disease. The HTT gene provides instructions for making a protein called huntingtin. This protein plays an important role in neurons in the brain. The HTT mutation that causes Huntington disease involves a DNA segment known as a CAG trinucleotide repeat. This segment is made up of a series of three DNA building blocks (cytosine, adenine, and guanine) that appear multiple times in a row. Normally, the CAG segment is repeated 10 to 35 times within the gene. In people with Huntington disease, the CAG segment is repeated 36 to more than 120 times. People with 36 to 39 CAG repeats may or may not develop the signs and symptoms of Huntington disease, while people with 40 or more repeats almost always develop the disorder. An increase in the size of the CAG segment leads to the production of an abnormally long version of the huntingtin protein. The elongated protein is cut into smaller, toxic fragments that bind together and accumulate in neurons, disrupting the normal functions of these cells. The dysfunction and eventual death of neurons in certain areas of the brain underlie the signs and symptoms of Huntington disease.

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. An affected person usually inherits the altered gene from one affected parent. In rare cases, an individual with Huntington disease does not have a parent with the disorder. As the altered HTT gene is passed from one generation to the next, the size of the CAG trinucleotide repeat often increases in size. A larger number of repeats is usually associated with an earlier onset of signs and symptoms. This phenomenon is called anticipation. People with the adult-onset form of Huntington disease typically have 40 to 50 CAG repeats in the HTT gene, while people with the juvenile form of the disorder tend to have more than 60 CAG repeats. Individuals who have 27 to 35 CAG repeats in the HTT gene do not develop Huntington disease, but they are at risk of having children who will develop the disorder. As the gene is passed from parent to child, the size of the CAG trinucleotide repeat may lengthen into the range associated with Huntington disease (36 repeats or more).

* **Joubert Syndrome:**

Joubert syndrome is a disorder that affects many parts of the body. The signs and symptoms of this condition vary among affected individuals, even among members of the same family.

The hallmark feature of Joubert syndrome is a combination of brain abnormalities that together are known as the [molar tooth sign](https://ghr.nlm.nih.gov/art/large/molar-tooth-sign.jpeg), which can be seen on brain imaging studies such as magnetic resonance imaging (MRI). This sign results from the abnormal development of structures near the back of the brain, including the cerebellar vermis and the brainstem. The molar tooth sign got its name because the characteristic brain abnormalities resemble the cross-section of a molar tooth when seen on an MRI.

Most infants with Joubert syndrome have low muscle tone (hypotonia) in infancy, which contributes to difficulty coordinating movements (ataxia) in early childhood. Other characteristic features of the condition include episodes of unusually fast (hyperpnea) or slow (apnea) breathing in infancy, and abnormal eye movements (ocular motor apraxia). Most affected individuals have delayed development and intellectual disability, which can range from mild to severe. Distinctive facial features can also occur in Joubert syndrome; these include a [broad forehead](https://ghr.nlm.nih.gov/art/large/broad-forehead.jpeg), [arched eyebrows](https://ghr.nlm.nih.gov/art/large/highly-arched-eyebrows.jpeg), droopy eyelids ([ptosis](https://ghr.nlm.nih.gov/art/large/ptosis.jpeg)), widely spaced eyes ([hypertelorism](https://ghr.nlm.nih.gov/art/large/hypertelorism.jpeg)), low-set ears, and a triangle-shaped mouth.

Joubert syndrome can include a broad range of additional signs and symptoms. The condition is sometimes associated with other eye abnormalities (such as retinal dystrophy, which can cause vision loss, and [coloboma](https://ghr.nlm.nih.gov/condition/coloboma), which is a gap or split in a structure of the eye), kidney disease (including [polycystic kidney disease](https://ghr.nlm.nih.gov/condition/polycystic-kidney-disease) and [nephronophthisis](https://ghr.nlm.nih.gov/condition/nephronophthisis)), liver disease, skeletal abnormalities (such as the presence of [extra fingers](https://ghr.nlm.nih.gov/art/large/polydactyly.jpeg) and toes), or hormone (endocrine) problems. A combination of the characteristic features of Joubert syndrome and one or more of these additional signs and symptoms once characterized several separate disorders. Together, those disorders were referred to as Joubert syndrome and related disorders (JSRD). Now, however, any instances that involve the molar tooth sign, including those with these additional signs and symptoms, are usually considered Joubert syndrome.

Joubert syndrome can be caused by mutations in more than 30 genes. The proteins produced from these genes are known or suspected to play roles in cell structures called primary cilia. Primary cilia are microscopic, finger-like projections that stick out from the surface of cells and are involved in sensing the physical environment and in chemical signaling. Primary cilia are important for the structure and function of many types of cells, including brain cells (neurons) and certain cells in the kidneys and liver. Primary cilia are also necessary for the perception of sensory input, which is interpreted by the brain for sight, hearing, and smell.

Mutations in the genes associated with Joubert syndrome lead to problems with the structure and function of primary cilia. Defects in these cell structures can disrupt important chemical signaling pathways during development. Although researchers believe that defective primary cilia are responsible for most of the features of these disorders, it is not completely understood how they lead to specific developmental abnormalities.

Mutations in the genes known to be associated with Joubert syndrome account for about 60 to 90 percent of all cases of this condition. In the remaining cases, the genetic cause is unknown.

Joubert syndrome typically has an [autosomal recessive pattern](https://ghr.nlm.nih.gov/art/large/autorecessive.jpeg) of inheritance, which means both copies of a gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they usually do not show signs and symptoms of the condition.

Rare cases of Joubert syndrome are inherited in an [X-linked recessive pattern](https://ghr.nlm.nih.gov/art/large/xlinkrecessive.jpeg). In these cases, the causative gene is located on the [X chromosome](https://ghr.nlm.nih.gov/chromosome/X), which is one of the two [sex chromosomes](https://ghr.nlm.nih.gov/art/large/sex-chromosomes-x-and-y.jpeg). In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

* **Ataxia-telangiectasia:**

Ataxia-telangiectasia is a rare inherited disorder that affects the nervous system, immune system, and other body systems. This disorder is characterized by progressive difficulty with coordinating movements (ataxia) beginning in early childhood, usually before age 5. Affected children typically develop difficulty walking, problems with balance and hand coordination, involuntary jerking movements (chorea), muscle twitches (myoclonus), and disturbances in nerve function (neuropathy). The movement problems typically cause people to require wheelchair assistance by adolescence.

People with this disorder also have slurred speech and trouble moving their eyes to look side-to-side (oculomotor apraxia). Small clusters of enlarged blood vessels called telangiectases, which occur in the eyes and on the surface of the skin, are also characteristic of this condition.

Affected individuals tend to have high amounts of a protein called alpha-fetoprotein (AFP) in their blood. The level of this protein is normally increased in the bloodstream of pregnant women, but it is unknown why individuals with ataxia-telangiectasia have elevated AFP or what effects it has in these individuals.

People with ataxia-telangiectasia often have a weakened immune system, and many develop chronic lung infections. They also have an increased risk of developing cancer, particularly cancer of blood-forming cells ([leukemia](https://ghr.nlm.nih.gov/art/large/abnormal-blood-cell-development-in-leukemia.jpeg)) and cancer of immune system cells ([lymphoma](https://ghr.nlm.nih.gov/art/large/lymphoma-stageii.jpeg)). Affected individuals are very sensitive to the effects of radiation exposure, including medical x-rays. The life expectancy of people with ataxia-telangiectasia varies greatly, but affected individuals typically live into early adulthood.

Mutations in the [ATM](https://ghr.nlm.nih.gov/gene/ATM) gene cause ataxia-telangiectasia. The ATM gene provides instructions for making a protein that helps control [cell division](https://ghr.nlm.nih.gov/art/large/mitosismeiosis.jpeg) and is involved in DNA repair. This protein plays an important role in the normal development and activity of several body systems, including the nervous system and immune system. The ATM protein assists cells in recognizing damaged or broken DNA strands and coordinates DNA repair by activating enzymes that fix the broken strands. Efficient repair of damaged DNA strands helps maintain the stability of the cell's genetic information.

Mutations in the ATM gene reduce or eliminate the function of the ATM protein. Without this protein, cells become unstable and die. Cells in the part of the brain involved in coordinating movements ([the cerebellum](https://ghr.nlm.nih.gov/art/large/parts-of-the-brain.jpeg)) are particularly affected by loss of the ATM protein. The loss of these brain cells causes some of the movement problems characteristic of ataxia-telangiectasia. Mutations in the ATM gene also prevent cells from responding correctly to DNA damage, which allows breaks in DNA strands to accumulate and can lead to the formation of cancerous tumors.

Ataxia-telangiectasia is inherited in an [autosomal recessive pattern](https://ghr.nlm.nih.gov/art/large/autorecessive.jpeg), which means both copies of the [ATM](https://ghr.nlm.nih.gov/gene/ATM) gene in each cell have mutations. Most often, the parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of the condition.

About 1 percent of the United States population carries one mutated copy and one normal copy of the ATM gene in each cell. These individuals are called carriers. Although ATM mutation carriers do not have ataxia-telangiectasia, they are more likely than people without an ATM mutation to develop cancer; female carriers are particularly at risk for developing [breast cancer](https://ghr.nlm.nih.gov/condition/breast-cancer). Carriers of a mutation in the ATM gene also may have an increased risk of heart disease.

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