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**Matric no: 17/MHS01/025**

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**Course: Neuroanatomy**

**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.



The cerebellum is located at the back of the brain, immediately inferior to the occipital and temporal lobes, and within the posterior cranial fossa. It is separated from these lobes by the tentorium cerebelli, a tough layer of dura mater.

It lies at the same level of and posterior to the pons, from which it is separated by the fourth ventricle.

During embryonic development, the anterior portion of the neural tube forms three parts that give rise to the brain and associated structures:

Forebrain (prosencephalon)

Midbrain (mesencephalon)

Hindbrain (rhombencephalon)

The hindbrain subsequently divides into the metencephalon (superior) and the myelencephalon (inferior). The cerebellum develops from the metencephalon division.

This article will focus on the anatomy of the cerebellum. It will provide a brief overview of its functions and development, and finally it will highlight the clinical relevance of cerebellar disorders.

**Genes** in the developing cerebellar primordium, 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. CHICK–QUAIL CHIMAERA experiments have indicated that both the mesencephalon and metencephalon contribute to the developing cerebellum. 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,
* Gbx2, a homologue of the Drosophila gene unplugged6

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 Otx2also regulate the expression of Fgf8 (fibroblast growth factor 8); Otx2negatively regulates Fgf8 expression, whereas Gbx2maintains it. Fgf8 is involved in regulating the various genes expressed in the mid- and hindbrain regions. (Mutant mice with a reduced level of Fgf8 expression have a severe patterning defect of the mid-/hindbrain region, which usually affects the cerebellum).

Fgf8 is a diffusible factor that exerts its action partially by inducing the expression of wingless homologue 1 (Wnt1) through Lim home box 1b (Lmx1b)16,17. Wnt1, in turn, maintains the expression of Engrailed (En1)18, which then positively regulates Fgf8 expression, completing the feedback regulatory loop . Mutants of Wnt1, En1 and Lmx1b all show patterning defects in the mid-/hindbrain region. Wnt1 and Lmx1b probably exert their influence through the action of En1. En2, a paralogue of En1, might also function in mid-/hindbrain patterning. En2 is expressed shortly after En1. Deletion of En2 against a haploinsufficient En1 mutant background was accompanied by a patterning defect in the mid-/hindbrain region more severe than that seen in a single mutant of En1; similarly, deletion of En1 against a haploinsufficient En2 mutant background also leads to an exaggerated phenotype21.

Although the cross-regulation between **Wnt1**, **En1** and **Fgf8** is beginning to be understood, several other genes that are not part of this pathway are also important in patterning of the mid-/hindbrain region. The paired box genes Pax2 and Pax5 are expressed in the mid-/hindbrain region. Pax2-null mice never develop a cerebellum or posterior mesencephalon. Although Pax5 mutants have only a mild phenotype in the mid-/hindbrain region, mice with a Pax5 mutation against a Pax2 sensitized background lack a cerebellum and posterior midbrain. Pax2 and Pax5 might also be involved in the regulation of En1, Wnt1 and other patterning genes, and together constitute another positive regulatory loop. The Hox gene family, which has an active role in patterning the hindbrain, seems to help to restrict the development of metencephalon structures into the myelencephalon. For example,Hoxa2 (home box A2), the most anteriorly expressed Hox gene, probably marks the caudal limit of the cerebellar anlage at rhombomere. Mice without Hoxa2 develop enlarged cerebella. Less is known about the dorsoventral patterning in this region. Bone morphogenetic proteins (Bmps) and sonic hedgehog (Shh) govern neuronal fates in the spinal cord; they have also been implicated in dorsoventral patterning of the mid-/hindbrain region. Bmps can induce the cerebellar granule neuron marker mouse atonal homologue 1 (Math1) when expressed in the ventral neural tube of the region, and ectopic expression of SHH in the chick dorsal neural tube leads to ventralization of the neural tube and disruption of the mid-/hindbrain region. Cerebellar development is also affected by ectopic expression of Shh, which leads to defects of the midline of the neural tube. In sum, the reciprocal repression of Otx2 and Gbx2 forms the IO, which in turn uses Fgf8 and En1 to pattern the prospective mid-/hindbrain region. Cells from both the mesencephalon and the metencephalon give rise to cerebellar tissues

**Cerebellar** **Disorders**

1. **Friedreich ataxia**

Friedreich ataxia is a genetic condition that affects the nervous system and causes movement problems. People with this condition develop impaired muscle coordination (ataxia) that worsens over time. Other features of this condition include the gradual loss of strength and sensation in the arms and legs; muscle stiffness (spasticity); and impaired speech, hearing, and vision. Individuals with Friedreich ataxia often have a form of heart disease called hypertrophic cardiomyopathy, which enlarges and weakens the heart muscle and can be life threatening. Some affected individuals develop diabetes or an abnormal curvature of the spine (scoliosis).

**Genetic Basis**

Mutations in the FXN gene cause Friedreich ataxia. This gene provides instructions for making a protein called frataxin. Although its role is not fully understood, frataxin is important for the normal function of mitochondria , the energy-producing centres within cells. One region of the FXN gene contains a segment of DNA known as a GAA trinucleotide repeat . This segment is made up of a series of three DNA building blocks (one guanine and two adenines) that appear multiple times in a row. Normally, this segment is repeated 5 to 33 times within the FXN gene. In people with Friedreich ataxia, the GAA segment is repeated 66 to more than 1,000 times. The length of the GAA trinucleotide repeat appears to be related to the age at which the symptoms of Friedreich ataxia appear, how severe they are, and how quickly they progress. People with GAA segments repeated fewer than 300 times tend to have a later appearance of symptoms (after age 25) than those with larger GAA trinucleotide repeats. The abnormally long GAA trinucleotide repeat disrupts the production of frataxin, which severely reduces the amount of this protein in cells. Certain nerve and muscle cells cannot function properly with a shortage of frataxin, leading to the characteristic signs and symptoms of Friedreich ataxia.

1. **Huntington** **disease**

Huntington disease is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition). 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.

**Genetic** **Basis**

Mutations in the HTT gene cause Huntington disease. The HTT gene provides instructions for making a protein called huntingtin. Although the function of this protein is unknown, it appears to play an important role in nerve cells (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.

1. **Niemann**-**Pick** **disease**

Niemann-Pick disease is a condition that affects many body systems. It has a wide range of symptoms that vary in severity. Niemann-Pick disease is divided into four main types: type A, type B, type C1, and type C2. These types are classified on the basis of genetic cause and the signs and symptoms of the condition.

**Genetic** **Basis**

Niemann-Pick disease types A and B is caused by mutations in the SMPD1 gene. This gene provides instructions for producing an enzyme called acid sphingomyelinase. This enzyme is found in lysosomes , which are compartments within cells that break down and recycle different types of molecules. Acid sphingomyelinase is responsible for the conversion of a fat (lipid) called sphingomyelin into another type of lipid called ceramide. Mutations in SMPD1 lead to a shortage of acid sphingomyelinase, which results in reduced break down of sphingomyelin, causing this fat to accumulate in cells. This fat build-up causes cells to malfunction and eventually die. Over time, cell loss impairs function of tissues and organs including the brain, lungs, spleen, and liver in people with Niemann-Pick disease types A and B. Mutations in either the NPC1 or NPC2 gene cause Niemann-Pick disease type C. The proteins produced from these genes are involved in the movement of lipids within cells. Mutations in these genes lead to a shortage of functional protein, which prevents movement of cholesterol and other lipids, leading to their accumulation in cells. Because these lipids are not in their proper location in cells, many normal cell functions that require lipids (such as cell membrane formation) are impaired. The accumulation of lipids as well as the cell dysfunction eventually leads to cell death, causing the tissue and organ damage seen in Niemann disease types C1 and C2.

1. **Leigh** **syndrome**

Leigh syndrome is a severe neurological disorder that usually becomes apparent in the 6rst year of life. This condition is characterized by progressive loss of mental and movement abilities (psychomotor regression) and typically results in death within two to three years, usually due to respiratory failure. A small number of individuals do not develop symptoms until adulthood or have symptoms that worsen more slowly. The 6rst signs of Leigh syndrome seen in infancy are usually vomiting, diarrhoea, and difficulty swallowing (dysphagia), which disrupts eating.

**Genetic** **Basis**

Leigh syndrome can be caused by mutations in one of more than 75 different genes. In humans, most genes are found in DNA in the cell's nucleus , called nuclear DNA. However, some genes are found in DNA in specialized structures in the cell called mitochondria . This type of DNA is known as mitochondrial DNA (tuna). While most people with Leigh syndrome have a mutation in nuclear DNA, about 20 percent have a mutation in mtDNA. Most genes associated with Leigh syndrome are involved in the process of energy production in mitochondria. Mitochondria use oxygen to convert the energy from food into a form cells can use through a process called oxidative phosphorylation . Five protein complexes, made up of several proteins each, are involved in this process. The complexes are named complex I, complex II, complex III, complex IV, and complex V. During oxidative phosphorylation, the protein complexes drive the production of adenosine triphosphate (ATP), the cell's main energy source, through a step-by-step transfer of negatively charged particles called electrons. Many of the gene mutations associated with Leigh syndrome affect proteins in these complexes or disrupt their assembly. These mutations reduce or eliminate the activity of one or more of these complexes, which can lead to Leigh syndrome.

1. **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.

**Genetic** **Basis**

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, Ginger-like projections that stick out from the surface of cells and are involved in sensing the physical environment and in chemical signalling. 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 signalling 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.

**Conclusion**

Explorations into the molecular basis of cerebellar development have begun to reveal how a simple segment of the neural tube becomes the nexus of all motor control. Mapping this developmental terrain in greater detail should not only give us an understanding of malformations that involve the cerebellum, but should allow us to understand problems of cell differentiation and migration. Medulloblastoma, for example, is one of the most common and aggressive tumours in children, and is thought to originate in the granule neurons or their precursors. Ultimately, of course, we hope that a greater understanding will yield viable therapies. And, although it is not yet possible to say what tangible fruits will be harvested from discovering the factors that govern Purkinje cell differentiation, for example, or the formation of cerebellar folia, we can eagerly anticipate the new directions in which such knowledge will undoubtedly take us.

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