**NEUROANATOMY ASSIGNMENT**

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**TOPIC: CEREBELLUM AND ITS CONNECTIONS**

**REVIEW ON THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM HIGHLIGHTING THE GENETIC BASES OF KNOWN CEREBELLAR DISORDERS.**

The cerebellum (“little brain”) is a structure that is located at the back of the brain, underlying the occipital and temporal lobes of the cerebral cortex. It is responsible for coordinating motor movements including balance and motor learning.

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.

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. Purkinje cells (PCs), Golgi neurons, stellate and basket cells all arise from the ventricular neuroepithelium.

Many genes like ***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**.

* **En 1 gene:** Engrailed (**En**) **1** is a homeobox **gene** that helps primarily regulate development **in** the cerebellum of humans. The expression of **En1** is regulated until 13 days after fertilization by Fgf8, which controls the development of the forebrain and hindbrain.
* **En 2 gene: En2** transcription factor is involved **in** patterning the midbrain **of** the central nervous system during embryonic development. Specifically, it is required for proper positioning **of** folia **in** the developing hemispheres. It continues to regulate foliation throughout nervous system development.

The engrailed homeobox genes are required in multiple cell lineages to coordinate sequential formation of fissures and growth of the cerebellum.

* **Pax 2 gene:** The *PAX2* gene belongs to a family of genes that plays a critical role in the formation of tissues and organs during embryonic development. The members of the PAX gene family are also important for maintaining the normal function of certain cells after birth. To carry out these roles, the PAX genes provide instructions for making proteins that attach to specific areas of DNA and help control the activity (expression) of particular genes. On the basis of this action, PAX proteins are called transcription factors.

During embryonic development, the ***PAX2* gene** provides instructions for producing a protein that is involved in the formation of the eyes, ears, brain and spinal cord (central nervous system), kidneys, urinary tract, and genital tract. After birth, the PAX2 protein is thought to protect against cell death during periods of cellular stress.

* **Wnt7b gene:** is a signaling **protein** that plays a crucial **role** for many developmental processes. The primary **role** of**Wnt7b** is to establish the cortico-medullary axis of epithelial organization within an organ.
* **Ephrins:** are a family of proteins that serve as the ligands of the eph receptors. Results identify Eph receptors and ephrins as the first molecules known to demarcate individual cerebellar lobules during development of the cerebellum**.**
* **Foxc1** **gene:** controls normal cerebellar and posterior fossa development by regulating secreted growth factor signals from the mesenchyme.

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.

**SOME CEREBELLAR DISORDERS AND THEIR GENETIC BASIS**

**Dandy Walker Malformation(DWM) :** DWM is characterized by underdevelopment (small size and abnormal position) of the middle part of the cerebellum known as the cerebellar vermis, cystic enlargement of the 4th ventricle and enlargement of the base of the skull (posterior fossa). DWM is sometimes (20-80%) associated with hydrocephalus, in which blockage of the normal flow of spinal fluid leads to excessive amounts of fluid accumulating in and around the brain. This leads to abnormally high pressure within the skull and swelling of the head, and can lead to neurological impairment. Mutations in FOXC1, a transcription factor gene located in the 6p25.3 locus, have recently been shown to contribute to human DWM.

**Joubert Syndrome:** It is characterized by the absence or underdevelopment of the cerebellar vermis (a part of the brain that controls balance and coordination) and a malformed brain stem (connection between the brain and spinal cord). **Mutations in the INPP5E gene, which codes for inositol polyphosphate-5-phosphatase E, were found in patients with Joubert syndrome.**

**Friedreich's ataxia** is a rare genetic disease that causes difficulty walking, a loss of sensation in the arms and legs, and impaired speech. It's also known as spinocerebellar degeneration. The disease causes damage to parts of your brain and spinal cord and can also affect your heart. “**Ataxia**” means lack of order. 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 centers within cells in the cerebellum.

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