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

**REVIEW ON THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM**

Developmental genetics is the study of how genes control the growth and development of an organism throughout its life-cycle.

The internal structure of the cerebellum reflects an intriguing paradox; its cytoarchitecture is relatively simple and repeated throughout, yet the connections between its neurons are wired into a complex array of gene expression domains and functional circuits. 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 lineage 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 repattern 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.

The development of the cerebellum can be described in four basic stages:

In the first stage, characterization of cerebellar territory occurs at the midbrain–hindbrain boundary. Transplantation studies in chicken and mouse have found that the isthmus organizer (IsO), a region corresponding to the midbrain–hindbrain boundary expression, is crucial for specifying midbrain and cerebellar structures. At the isthmus, restricted expression of secreted factors, such as fibroblast growth factor 8, *FGF8* and *Wnt1*, the mammalian homolog of *Drosophila* wingless gene, as well as homeobox proteins (*En1* and *En2)* and paired box genes *Pax2* and *Pax5* are required for early specification of midbrain and hindbrain structures.

In the second stage, two compartments for cell proliferation are formed. Purkinje cells and cells of the deep cerebellar nuclei are generated in the roof of the fourth ventricle, and granule cell precursors, as well as cells of the precerebellar nuclei are formed in the rhombic lip. Development of Purkinje cells is not well understood, but they are known to secrete sonic hedgehog which regulates proliferation of granule cells. By this time point, granule neuron precursors express a number of markers, *Math1, nestin, zipro1/RU49* and *Zic* genes 1, 2. Purkinje cells migrate radially to their final positions, whereas granule neurons migrate over the surface of the developing cerebellum, forming the external granule layer (EGL).

In the third stage, cells of the EGL migrate inward along the processes of Bergman glia to their final position in the internal granular layer (IGL).

Finally, cerebellar circuitry is established and further differentiation occurs. The lower portion of the rhombic lip also gives rise to cells of the precerebellar nuclei such as the inferior olivary nuclei, which migrate to positions in the brainstem

**Genetic Basis of Known Cerebellar Disorders includes**;

**VLDLR- associated Cerebellar hypoplasia**: it is an inherited condition that affects the development of the brain. People with this condition have unusually small and underdeveloped cerebellum, and this leads to problems with balance and coordination that become apparent in infancy and remain stable over time.

It results from mutations in the VLDLR gene. This gene provides instructions for making a protein called a very low density lipoprotein (VLDL) receptor. Starting before birth, this protein plays a critical role in guiding the movement of developing nerve cells to their appropriate locations in the brain. Mutations which occur in the VLDLR gene prevent the cells from producing any functional VLDL receptor protein. Without this protein, developing nerve cells cannot reach the parts of the brain where they are needed.

**Joubert syndrome**: it is a disorder which affects many parts if the body and the signs and symptoms vary among affected individuals, even among members of the same family. The hallmark feature of this condition is a combination of brain abnormalities that are together known as the molar tooth sign, which can be seen on brain imaging studies such as magnetic resonance imaging (MRI)

Joubert syndrome can be caused by mutations in more than 30 genes. The proteins from these genes are known or suspected to play roles in cell structures called primary cilia which are microscopic, fingerlike 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 in 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.

**Friedreich’s Ataxia**: It is a rare genetic disease that causes difficulty in walking, a loss of sensation in the arms and legs and impaired speech. It is also known as spinocerebellar degeneration. The disease causes damage to parts of the brain and spinal cord and can also affect the heart.

Friedreich’s ataxia is a genetic defect that is inherited from both parents by autosomal recessive transmission. The disease is linked to a gene called FXN which normally causes the body to produce up to 33 copies of a specific DNA sequence. In people with Friedreich’s ataxia, this sequence may repeat 66 to over 1000 times. When production of this DNA sequence spirals out of control, severe damage to the brain’s cerebellum and spinal cord can result.

**Reference**

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