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QUESTION;

1. **Write a concise review on the developmental genetics of the cerebellum and highlights the genetic bases of known cerebellar disorder.**

**Answers.**

The cerebellum develops from the dorsal region of the posterior neural tube, and its cells arise from two germinal matrices. The function is to coordinate muscle movements and maintain posture and balance.

It is one of the first structures of the brain to begin to differentiate and one of the last to mature. Even after birth, it continues to grow for some months. 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. 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 Shh 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.

Cerebellar disorders is a statement used to refer to problems of the Cerebellum, an area in the brain that controls balance and coordination.

They include;

1. **Dandy-Walker syndrome**: A congenital anomaly relating to the Cerebellar Vermis, is a rare congenital brain malformation in which the part joining the two hemispheres of the cerebellum (the cerebellar vermis) does not fully form, and the fourth ventricle and space behind the cerebellum (the posterior fossa) are enlarged with cerebrospinal fluid. It is characterized by an underdevelopment of the Cerebellar vermis,. A distinguishing symptom is Hydrocephalus. The cause for some patients has been as a result of chromosome abnormalities including deletion of chromosome 3q24.3, 6p25 or 13q32.2-q33.2, or duplication of 9p.

2. **Cerebellar Hypoplasia**: a neurological condition in which the cerebellum is smaller than usual or incompletely developed. It is a feature of a number of congenital malformation syndromes, such as Walker-Warburg syndrome. It is said to be due to a defect in the neuronal proliferation and neuronal migration during the development of the embryonic nervous system. Symptoms in infants may include; problems with walking and balance, seizures, and intellectual disability.

3**. Joubert Syndrome**: is disorder of brain development that may affect many parts of the body. A condition characterized by the absence or underdevelopment of the cerebellar vermis in addition to a malformed brain stem. The most common features of in infants include abnormally rapid breathing, abnormal eye movements, hypotonia. Etc. In most cases, Joubert syndrome is inherited in an autosomal recessive manner.

4. **Machado-Joseph Disease**: an autosomal dominant neurodegenerative disease causing progressive Cerebellar Ataxia, resulting in a lack of motor control and coordination. This disease is a result of a genetic mutation that causes an expansion of abnormal ‘CAG’ trinucleotide which eventually forms an abnormal form of the protein Ataxin that causes the degeneration of the cells of the hindbrain.

5. **Huntington diseases**: is a fatal genetic disorder that causes the progressive breakdown of nerve cells in the brain. It deteriorates a person’s physical and mental abilities usually during their prime working years and has no cure. Symptoms usually appear between the ages of 30 to 50, and worsen over a 10 to 25-year period. They include Personality changes, mood swings & depression, Slurred speech, difficulty in swallowing & significant weight loss.