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QUESTION 1: Write a concise review on the developmental genetics of the cerebellum and highlight the genetic basis of known cerebellar disorders.

ANSWER: The cerebellum is an important structure in the nervous system that controls and regulates motor and non-motor functions. The cerebellum is the Latin word for little brain. It is in the posterior cranial fossa, beneath the occipital lobe and dorsal to the brainstem. It is involved in the regulation of posture, motor coordination, balance, and motor learning. More recently, it has been proposed that it plays a role in emotion and cognition. The cerebellum consists of a midline region referred to as the vermis, a narrow paravermal area immediately adjacent to the vermis, and large hemispheres on either side. Well-defined fissures divide the cerebellum into an anterior, posterior and flocculonodular lobe.

 During prenatal development the nervous system, the central nervous system originates from the area of the ectoderm known as the neural plate. Thee neural plate thickens as a result of cell proliferation and then begins to invaginate and thus forms the neural groove. The invagination of the neural groove continues until the lateral edges of the neural groove fuse to form the neural tube through a process called neurulation. As the edges of the neural groove fuse to form the neural tube, which detaches from the ectoderm, a population of neuroectodermal cells dissociate from the neural fold as neural crest cells. The rostral end of the neural tube develops into the prosencephalon, mesencephalon, and rhombencephalon. The cerebellum develops from the dorsal portion of the metencephalon (which is one of the two divisions of the rhombencephalon, the other being myelencephalon) and the neural folds. The alar plates of the rostral metencephalon undergo bilateral expansion in the dorsolateral region to form the rhombomere 1. These rostral extensions of alar plate eventually join in the midline to form the vermis of the cerebellum, as the cerebellum begins to form, initially from the dorsal rhombomere 1 (r1), it rotates 90o before fusing at the midline as the vermis. This rotation of the dorsal r1 results in the conversion of rostral-caudal axis seen in the early neural tube, into the medial-lateral axis seen in the mature cerebellum. As the bilateral cerebellar primordia fuse, the midline vermis is derived from the rostro-medial ends while the cerebellar hemispheres are derived from the more caudo-lateral components of the rhombencephalon.

 The isthmic organizer formed at the midbrain-hindbrain boundary induces the cerebellar plate in the dorsal r1. Cerebellar cells are generated in two distinct germinal zones in r1. The ventricular zone of the cerebellar plate expresses the basic helix-loop-helix transcription factor Ptfla. Ptfla+ progenitors produce GABAergic neurons of the cerebellar cortex (Purkinje cells and interneurons) and of the deep cerebellar nuclei. The rhombic lip at the dorsal margin of r1 expresses another basic helix-loop-helix factor, Atoh1 (also known as Math1) Atoh1+ progenitors generate glutamatergic neurons including granule cells, unipolar brush cells and large deep cerebellar nuclei projection neurons. Two factors promote the self-formation of cerebellar plates, the FGF19 and the SDF1. FDF19 promotes spontaneous formation of hindbrain neural tube-like neuroepithelial structures with dorsal to ventral polarity. The FDF19 and the SDF1 induces the generation of continuous cerebellar plate neuroepithelium that differentiates into a multilayered structure.

**GENETIC BASIS OF KNOWN CEREBELLAR DISORDERS**

 Cerebellar disorders can be due to trauma, hemorrhage, tumors, and some can be congenital. Some examples of cerebellar disorders are: Ataxia, Joubert syndrome, Dandy-Walker syndrome, Machado-Joseph disease, Olivopontocerebellar atrophy etc.

1. **Hereditary ataxias**

 Hereditary ataxias may be autosomal recessive or autosomal dominant. Autosomal recessive ataxias include Friedreich ataxia (the most prevalent), ataxia-telangiectasia, abetalipoproteinemia, ataxia with isolated vitamin E deficiency, and cerebrotendinous xanthomatosis.

* **Friedreich ataxia** results from a gene mutation causing abnormal repetition of the DNA sequence GAA in the *FXN* gene on the long arm of chromosome 9; the *FXN* gene codes for the mitochondrial protein frataxin. The GAA sequence is repeated 5 to 38 times within the *FXN* gene in people who do not have Friedreich ataxia; however, in people with Friedreich ataxia, the GAA sequence may be repeated 70 to > 1000 times. Inheritance is autosomal recessive. Decreased frataxin levels lead to mitochondrial iron overload and impaired mitochondrial function. In Friedreich ataxia, gait unsteadiness begins between ages 5 and 15; it is followed by upper-extremity ataxia, dysarthria, and paresis, particularly of the lower extremities. Mental function often declines. Tremor, if present, is slight. Reflexes and vibration and position senses are lost. Talipes equinovarus (clubfoot), scoliosis, and progressive cardiomyopathy are common. By their late 20s, patients may be confined to a wheelchair. Death, often due to arrhythmia or heart failure, usually occurs by middle age.
* **Spinocerebellar ataxias** **(SCAs)** are the main autosomal dominant ataxias. Classification of these ataxias has been revised many times recently as knowledge about genetics increases. Currently, at least 43 different gene loci are recognized; about 10 involve expanded DNA sequence repeats. Some involve a repetition of the DNA sequence CAG that codes for the amino acid glutamine, similar to that in Huntington disease. Manifestations of SCAs vary. Some of the most common SCAs affect multiple areas in the central and peripheral nervous systems; neuropathy, pyramidal signs, and restless leg syndrome, as well as ataxia, are common. Some SCAs usually cause only cerebellar ataxia.

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1. **JOUBERT SYNDROME:** This is a rare brain malformation characterized by the absence or underdevelopment of the cerebellar vermis (an area of the brain that controls balance and coordination) as well as a malformed brain stem. Features of the Joubert syndrome in infants include abnormally rapid breathing, decreased muscle tone, abnormal eye movements, impaired intellectual development and inability to coordinate voluntary muscle movements. This syndrome can be caused by mutations in more than 30 genes some of which are: AHI1, ARL13B, OFD1, B9D1, C2CD3, TCTN1, MKS1, NPHP1, ZNF423, B9D2 etc. mutations in these genes leads to problems with the structure and function of the primary cilia (which is necessary for perception of sensory input). This syndrome has an autosomal recessive pattern of inheritance which means both copies of a gene in each cell have mutations. Rare cases are inherited in an X-linked recessive pattern which mostly affects males.
2. **DANDY**-**WALKER SYNDROME:** This is a congenital brain malformation involving the cerebellum and the fluid-filled spaces around it. There is an enlargement of the 4th ventricle, a partial or complete absence of the area of the brain between the 2 cerebellar hemispheres and cyst formation near the lowest part of the skull. Dandy-walker malformation most often occurs in people with trisomy 18 (an extra copy of chromosome 18) but can also occur in people with trisomy 13, trisomy 21. This condition can also be associated with deletion or duplication of certain chromosomes. Some genes associated with this syndrome are: FOXC1, ZIC1, ZIC4. Most cases of this syndrome are sporadic i.e. they occur in people with no history of the disorder in their family. It does not have a clear pattern of inheritance.
3. **MACHADO**-**JOSEPH DISEASE:** Machado-Joseph disease which is also called spinocerebellar ataxia type 3, is a rare hereditary ataxia. The disease is characterized by slowly progressive clumsiness and weakness in arms and legs, spasticity, a staggering lurching gait easily mistaken for drunkenness, difficulty with speech, swallowing, involuntary eye movements, double vision and frequent urination. This disease is classified as one of many dominantly inherited ataxia specifically the spinocerebellar ataxia. Machado-Joseph disease belongs to a class of genetic disorders called expanded repeat diseases. Mutations in expanded repeat diseases are abnormally long repeats of a normal repetition of three letters of the DNA genetic code. In the case of this disease, the code sequence “CAG” is repeated in the ATXN3 gene, which produces the disease protein called ataxin-3. This protein when mutated is prone to fold abnormally and accumulate in the affected brain cells. They are located in the nucleus of the cell.
4. **OLIVOPONTOCEREBELLAR ATROPHY (OPCA)**: This is a term that describes the degeneration of neurons in specific areas of the brain- the cerebellum, pons and inferior olives. OPCA is present in several neurodegenerative syndromes, including inherited and non-inherited forms of ataxia. OPCA can occur in association with disorders caused by inherited genetic mutations or it can be sporadic. The genetic form of OPCA may be inherited in an autosomal dominant, autosomal recessive or X-linked manner. The inheritance pattern depends on the specific genetic cause. OPCA associated with spinocerebellar ataxia 3 is caused by a mutation in the ATXN3 gene and is inherited in an autosomal dominant manner.

**References**

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