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**DEPARTMENT: MEDICINE AND SURGERY**

**COURSE: NEUROANATOMY**

**COURSE CODE: ANA 303**

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

**ANSWER:**

**Introduction**: The cerebellum represents about 10% of the total brain volume hence it is reffered to as little brain. The mature cerebellum contains more than half of our neurons. It is therefore no surprise that the cerebellum has a central role in our daily living. The cerebellum acts as a coordination centre, using sensory inputs from the periphery to fine-tune our movement and balance. During early neurogenesis, rostrocaudal patterning by intrinsic and extrinsic factors, such as Otx2, Gbx2 and Fgf8, plays an important role in the positioning and formation of the cerebellar primordium.

**Overview of human Cerebellar development**: The cerebellum is derived from dorsal rhombomere 1, which comprises the most anterior aspect of the hindbrain. Expression of the homeobox genes Otx2 and Gbx2 are essential for the development of the midbrain and hindbrain. During development, these two genes are expressed in abutting domains where they antagonize each other to establish the mid/hindbrain boundary and formation of an isthmic organizer (IsO). The IsO functions as a classic signaling center by secreting fibroblast growth factor 8 (FGF8), which maintains the posterior border of Otx2 expression and is crucial for normal cerebellar development. FGF expression is strongly controlled during hindbrain development and its loss results in the absence of the midbrain and cerebellum. Accordingly, FGF expression is required for cell survival and to regulate gene expression in the mid/hindbrain region. Different mediolateral and anteroposterior regions of the midbrain and cerebellum require varying levels and durations of FGF signaling for proper development. For instance, a slight reduction in FGF8 signaling results in a specific loss of posterior midbrain and the vermis. A number of other genes cooperate with FGF8 to control cerebellar development. Among these are the homeobox genes, engrailed 1 (En1) and engrailed 2 (En2), and the paired box genes Pax2 and Pax5. Pax2 induces FGF8 expression while En1 and En2 are necessary for its maintenance. Interestingly, notch signaling may be upstream of all the above-mentioned genes during the establishment of the IsO. Although a great deal of attention has been given to FGF8, other members of the FGF family are also crucial for cerebellar development (e.g., FGF17 and FGF18) and several of the mRNAs that encode FGF signaling molecules exhibit a patterned expression postnatally.

**Genetic bases of some cerebellar disorders:**

1) Ataxia-telangiectasia: is a rare inherited disorder that affects the nervous system, immune system, and other body systems. Mutation in the ATM gene causes ataxia-telangiectasia. The ATM gene provides instructions for making protein that help control cell division. Mutation in the ATM gene eliminates the functions of the ATM protein. Without this protein, cells in the part of the brain involved in coordinating movement (the cerebellum) are particularly affected. The loss of these brain cells causes some of the movement problems involved with Ataxia. Children affected with Ataxia develop difficulty walking, problem with balance and coordination, involuntary jerking movement and disturbances in nerve function.

2) Disrupted WNT Signaling in Joubert Syndrome: Joubert syndrome is characterized by cerebellar vermis hypoplasia and abnormal superior cerebellar peduncles. It is associated with both movement disorders and mental retardation. Joubert syndrome is caused by mutations in the AHI1 (Abelson helper integration site 1)

3) Cerebellar hypoplasia: Cerebellar hypoplasia is a neurological condition in which the cerebellum is not completely developed or is smaller than it should be. Cerebellar hypoplasia is due to a defect in the neuronal proliferation and neuronal migration during development of the embryonic nervous system. It may occur with a variety of congenital syndromes, metabolic disorders and neurodegenerative disorders. Patients with trisomy 18, trisomy 21, and patients suffering from the autosomal recessive acro-callosal syndrome, these patients showed callosal agenesis with cerebellar hypoplasia.

4) Pontocerebellar hypoplasia: is a heterogeneous group of rare [neurodegenerative disorders](https://en.wikipedia.org/wiki/Neurodegeneration) caused by genetic [mutations](https://en.wikipedia.org/wiki/Mutation) and characterised by progressive [atrophy](https://en.wikipedia.org/wiki/Atrophy) of the [cerebellum](https://en.wikipedia.org/wiki/Cerebellum) or [brainstem](https://en.wikipedia.org/wiki/Brainstem) (particularly the [pons](https://en.wikipedia.org/wiki/Pons%22%20%5Co%20%22Pons)). Pontocerebellar hypoplasia is caused by mutation in gene TSEN2 (tRNA-splicing endonuclease 2), TSEN34, RARS2, TSEN54 (PCH2 and PCH4).

5) Cerebellar atrophy (degeneration): Cerebellar degeneration is a condition in which cerebellar cells, otherwise known as [neurons](https://en.wikipedia.org/wiki/Neuron), become damaged and progressively weakens in the [cerebellum](https://en.wikipedia.org/wiki/Cerebellum). There are two types of cerebellar degeneration; [paraneoplastic cerebellar degeneration](https://en.wikipedia.org/wiki/Paraneoplastic_cerebellar_degeneration%22%20%5Co%20%22Paraneoplastic%20cerebellar%20degeneration), and alcoholic or nutritional cerebellar degeneration.

**References:**

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