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**COURSE TITLE: NEUROANATOMY**

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**ASSIGNMENT TITLE: CEREBELLUM AND ITS CONNECTIONS**

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

The cerebellum represents 10% of the brain's total volume, but contains more than half of our neurons. It acts as a coordination centre, using sensory inputs from the periphery to fine-tune our movement and balance. 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. The study of mouse homologues of *Drosophila* genes has provided valuable insights into the molecular basis of cerebellar development. 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. The mesencephalon and metencephalon both contribute to the developing mouse cerebellum. The patterning of these two regions depends on signals from the isthmus organizer (IO), located just caudal to their junction. *Otx2* and *Gbx2* are central to IO development. *Otx2* is expressed in the mesencephalon, with a posterior boundary at the rostral metencephalon; *Gbx2* is expressed in the metencephalon, and its anterior boundary abuts the *Otx2* boundary. Reciprocal repression maintains a sharp boundary between these domains. *Otx2* and *Gbx2* form part of a regulatory loop that includes *Wnt1*, *En1* and *Fgf8*. Many other genes, including members of the Pax and Hox families, are also involved in patterning this region. 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 S*hh* 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.

**GENETIC BASES OF KNOWN CEREBELLAR DISORDERS**

The mature cerebellum has exquisite, stereotypical morphology, foliation, and lamination, which are consistent between individuals and highly conserved across vertebrates. At the cellular level, unlike other regions of the CNS, the cerebellum is composed of very few neuronal types, each with distinct morphology, arranged in discrete lamina, and connected in stereotypical circuits. The cerebellum has essential roles in motor coordination, but is not essential for viability. Thus, compared with other regions of the central nervous system (CNS) the cerebellum has been more amenable to genetic studies since disruptions in development, which lead to abnormal morphology or function, are readily observed in obvious neurological and behavioral phenotypes. Because of this, it has been possible to obtain a precise understanding of cerebellar development .The mechanisms deciphered from the study of cerebellar development have broad applicability to other CNS regions such as the cerebral cortex. For example, while initial insights regarding the function of the Reelin gene were gleaned from studying the cerebella of reeler mice , recent studies have revealed that this gene is required for the emigration of dentate gyrus progenitors from a transient subpial zone and into the subgranular zone . Also, while Foxc1 controls normal cerebellar and posterior fossa development by regulating secreted growth factor signals from the mesenchyme , it is also required for the development of meningeal structures that in turn influence skull and cortical development

Causative genes include those involved in cerebellar patterning, cell fate specification, and other developmental processes

List of genes and suspected cellular processes that have been implicated in human cerebellar malformations (see text for discussion)

| **Cerebellar malformations** | **Implicated human genes** | **Likely disrupted process** |
| --- | --- | --- |
| Cerebellar vermis hypoplasia (CVH) | *OPHN1*  | Spine morphogenesis |
| Dandy–Walker malformation (DWM) | *ZIC1*, *ZIC4*, *FOXC* | Granule cell differentiation |
| Joubert syndrome and related disorders (JSRD) | *AHI1*, *ARL13B*, *CCD2A*, *CEP290*, *INPP5E*, *NPHP1*, *RPGRIP1L*, and *TMEM67*  | Granule cell proliferation |
| Pontocerebellar hypoplasia (PCH) | *CASK*, *RARS2*, *TSEN54*, *TSEN34*, and *TSEN2*  | Spine development, cell proliferation, tRNA splicing, cellular maintenance. |

**REFERENCES**

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