NAME: GWAIVANGMIN ZUMSHOK DORCAS MATRIC NUMBER: 17/MHS01/137 COURSE: ANA 303 DATE: 12TH JULY, 2020

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

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

Purkinje cells, Golgi neurons, stellate and basket cells all arise from the ventricular neuroepithelium. Purkinje cells are born around embryonic day 13, and they migrate along radial glial fibres into the cerebellar anlage. During their final maturation phase, Purkinje cells develop extensive dendritic arbors and synapse onto granule neurons. This depends on granule neuron signals, probably including *Wnt3* gene. Various growth factors are required for Purkinje cells 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 Purkinje cells. Purkinje cells 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* gene 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.

**Some known cerebellar disorders include:**

* **Joubert syndrome (JS)** which is an autosomal recessive neurodevelopmental disorder, which is characterized by the molar tooth malformation (MTM), a complex brainstem malformation that reflects aplasia or marked hypoplasia of the cerebellar vermis, thickened and elongated superior cerebellar peduncles and a deepened interpeduncular fossa. JS is genetically heterogeneous and so far three genetic loci have been mapped to 9q34.3 (JBTS1: OMIM 213300), 11p12–q13.3 (JBTS2: OMIM 608091) and 6q23 (JBTS3: 608629). JBTS1 appears to represent the classic Joubert phenotype of pure cerebellar and midbrain–hindbrain junction involvement, although the JBTS3 gene is also associated with cerebral cortical abnormalities, most notably polymicrogyria. JBTS2, in addition to classical JS features, is associated with a variety of other organ systems, involving kidney, eye and liver. Mutations of AHI1 have recently been shown to cause a form of JS, but the function of this gene is currently unknown.
* **Nephronophthisis (NPHP)** is a kidney disorder that represents the most common heritable cause of end-stage renal disease in children and is characterized by tubular atrophy, interstitial fibrosis and development of renal cysts. There are five genes (nephrocystin 1–5) known to cause several forms of NPHP. Juvenile NPHP is most often caused by mutations in NPHP1, encoding nephrocystin. The most common mutation is a homozygous deletion that spans three contiguous genes. Conversely, cerebellar malformations have been identified in patients diagnosed with NPHP.
* **Bardet–Biedl syndrome** (BBS: OMIM 209900) is characterized by obesity, mental retardation, polydactyly, gonadal malformation, retinal dystrophy and renal dysfunction. Neurological malformations are unusual, but cerebellar abnormalities have been reported. Eight genes, BBS1–BBS8, have been identified to date and all of the encoded proteins have been localized to cilia and or implicated in ciliary function and assembly, including cytoskeletal reorganization and cytokinesis. In particular, BBS4 has been associated with components of IFT, a microtubule-dependent mechanism by which components are trafficked during assembly and maintenance of cilia and flagella

**REFERENCES** <https://academic.oup.com/hmg/article/14/suppl_2/R235/663262> <https://www.nature.com/articles/35081558> <https://scholar.google.com/scholar?hl=en&as_sdt=0,5&qsp=1&q=genetic+basis+cerebellar+development&qst=br>