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**Question: Write a concise review on the developmental genetics of the cerebellum and highlight the genetical 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 co-ordination 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 rhombic lip is a posterior section of the developing metencephalon which can be recognized transiently within the vertebrate embryo).

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 (orthodenticle homeobox 2) and Gbx2 (gastrulation brain homeobox) 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 leans on 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(engrailed homeobox 1) and Fgf8 (fibroblast growth factor 8) 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 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 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.

**Cerebellar disorders**

1. **Nephronophthisis (NPHP):** This is a disorder that affects the kidneys. It is characterized by inflammation and scarring (fibrosis) that impairs kidney function. These abnormalities lead to increased urine production (polyuria), excessive thirst (polydipsia), general weakness, and extreme tiredness (fatigue). In addition, affected individuals develop fluid-filled cysts in the kidneys, usually in an area known as the corticomedullary region. Another feature of nephronophthisis is anemia ( shortage of red blood cells).

Nephronophthisis eventually leads to end-stage renal disease (ESRD), a life-threatening failure of kidney function that occurs when the kidneys are no longer able to filter fluids and waste products from the body effectively.

Nephronophthisis has several genetic causes, which are used to split the condition into distinct types. Nephronophthisis type 1, which is the most common type of the disorder and one cause of juvenile nephronophthisis, results from changes affecting the **NPHP1 gene**. The proteins produced from NPHP1 and the other genes involved in nephronophthisis are known or suspected to play roles in cell structures called cilia. Cilia are microscopic, finger-like projections that stick out from the surface of cells and are involved in chemical signaling.

The genetic mutations involved in nephronophthisis are thought to impair the structure or function of cilia in some way, which likely disrupts important chemical signalling pathways during development. 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.

1. **Joubert syndrome**: Joubert syndrome is a disorder that affects many parts of the body. The signs and symptoms of this condition vary among affected individuals, even among members of the same family. The hallmark feature of Joubert syndrome is a combination of brain abnormalities that together are known as the molar tooth sign, which can be seen on brain imaging studies such as magnetic resonance imaging (MRI). This sign results from the abnormal development of structures near the back of the brain, including the cerebellar vermis and the brainstem. The molar tooth sign got its name because the characteristic brain abnormalities resemble the cross-section of a molar tooth when seen on an MRI**.**

Joubert syndrome can be caused by mutations in more than 30 genes. The proteins produced from these genes are known or suspected to play roles in cell structures called primary cilia. Primary cilia are microscopic, finger-like projections that stick out from the surface of cells and are involved in sensing the physical environment and in chemical signalling. Mutations in the genes associated with Joubert syndrome lead to problems with the structure and function of primary cilia. Defects in these cell structures can disrupt important chemical signalling pathways during development.

. Mutations of AHI1 (Abelson Helper Integration Site) have recently been shown to cause a form of JS, but the function of this gene is currently unknown

1. **Bardet–Biedl syndrome:** Bardet-Biedl syndrome (BBS) is a genetic condition that impacts multiple body systems. It is classically defined by six features. Patients with BBS can experience problems with obesity, specifically with fat deposition along the abdomen. They often also suffer from intellectual impairments. Commonly, the kidneys, eyes and function of the genitalia will be compromised. People with BBS may also be born with an extra digit on the hands. The severity of BBS varies greatly even among individuals within the same family.

BBS can be caused by changes (mutations) in more than 20 different genes. It is usually inherited as an autosomal recessive condition. There are many gene mutations that are known to lead to the development of BBS, some of which are: BBS1, BBS2, ARL6 (BBS3), BBS4, BBS5, MKKS (BBS6), BBS7, TTC8 (BBS8), BBS9, BBS10, TRIM32 (BBS11), BBS12,MKS1 (BBS13), CEP290 (BBS14)

Patients with mutations in the BBS1 gene seem to have milder ophthalmologic involvement. In comparison, patients with mutations in the BBS2, BBS3 and BBS4 genes experience classic deterioration of their vision. Patients with mutations in the BBS10 gene generally have significantly increased tendency to obesity and insulin resistance.

**References**

<https://www.nature.com/articles/35081558>

<https://ghr.nlm.nih.gov/condition/nephronophthisis#genes>

<https://ghr.nlm.nih.gov/condition/joubert-syndrome#genes>

<https://rarediseases.org/rare-diseases/bardet-biedl-syndrome/>