NAME: **AJAYI EMMANUEL OLUWASEGUN**

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DEPARTMENT: **MEDICINE & SURGERY**

**DEVELOPMENTAL GENETICS OF THE CEREBELLUM**

The cerebellum represents 10% of the brain's total volume, but contains more than half of the neurons. It acts as a coordination center, 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.

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 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 fibers 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.

**Some known disorders of the cerebellum include:**

**Dandy-Walker Syndrome**

Dandy-Walker Syndrome is a congenital brain malformation that primarily affects development of the cerebellum. In individuals with this condition, the central part of the cerebellum (the vermis) is absent or very small and may be abnormally positioned. The cerebellar hemispheres may be small as well. In affected individuals, the fourth ventricle and the posterior cranial fossa are abnormally large. These abnormalities often result in problems with movement, coordination, intellect, mood and other neurological functions.

Dandy-Walker Malformation typically affects only the brain, but problems in other systems can include heart defects, malformations of the urogenital tract, extra fingers/toes (polydactyly) or fused fingers (syndactyly), or abnormal facial features.

Problems related to hydrocephalus or complications of its treatment are the most common cause of death in people with DWM. It is estimated to affect 1 in 10,000 to 30,000 newborns.

***Causes***

Researchers have found mutations in a few genes [FOXC1, ZIC1, and ZIC4] that are thought to cause Dandy-Walker Syndrome, but these mutations account for only a small number of cases. Dandy-Walker malformation has also been associated with many chromosomal abnormalities. This condition can feature of some conditions in which there is there is an extra copy of one chromosome in each cell (trisomy). DWM most often occurs in people with trisomy 18, but can also occur in people with trisomy 13, trisomy 21 and trisomy 9. This condition can also be associated with missing (deletions) or copied (duplications) pieces of certain chromosomes. It can also be a feature of genetic syndromes that are caused by mutations in specific genes.

**VLDLR-associated cerebellar hypoplasia**

VLDLR-associated cerebellar hypoplasia is a rare brain malformation that affects the development of the brain. People with this condition have an unusually small and underdeveloped cerebellum. This brain malformation leads to problems with balance and coordination (ataxia) that become apparent in infancy and remain stable over time.

Additional features of VLDLR-ACH include moderate to profound intellectual disability, impaired speech (dysarthria) or a lack of speech, and eyes that don’t look in the same direction (strabismus). This condition is inherited in an autosomal recessive pattern.

***Causes***

As the name suggests, VLDLR-associated cerebellar hypoplasia results from mutations in the VLDLR gene. This gene provides instructions for making a protein called a very low density lipoprotein (VLDL) receptor. Starting before birth, this protein plays a critical role in guiding the movement of developing nerve cells to their appropriate locations in the brain. Mutations in the VLDLR gene prevent cells from producing any functional VLDL receptor protein. Without this protein, developing nerve cells cannot reach the parts of the brain where they are needed. The resulting problems with brain development lead to ataxia and the other major features of this condition.

**Joubert Syndrome**

This is a rare brain malformation characterized by the absence or underdevelopment of the cerebellar vermis as well as a malformed brainstem (molar tooth sign). Most infants with Joubert syndrome have low muscle tone (hypoplasia) in infancy, contributes to difficulty coordinating movements (ataxia) in early childhood. Other characteristic features of the condition include episodes of unusually fast (hyperpnea) or slow (apnea) breathing in infancy, abnormal eye movements (ocular motor apraxia) and impaired intellectual development. Physical deformities may be present, such as extra fingers and toes (polydactyly), cleft lip/palate, ptosis, hypertelorism and tongue abnormalities. Kidney and liver abnormalities can develop, and seizures may also occur.

Joubert syndrome is estimated to affect between 1 in 80,000 and 1 in 100,000 newborns. Many cases of Joubert Syndrome are sporadic (not inherited). It typically has an autosomal recessive pattern of inheritance.

***Causes***

Joubert syndrome can be caused by mutations in more than 30 genes, some of which are AHI1, ARL13B, CCD2A, CEP290, INPP5E, NPHP1, RPGRIP1L and TMEM67. The proteins produced from these genes are known or suspected to play roles in cell structures called primary cilia. Primary cilia are important for the structure and function of many types of cells, including brain cells (neurons) and certain cells in the kidneys and liver.

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 signaling pathways during development. Mutations in the genes known to be associated with Joubert Syndrome account for about 60 to 90 percent of all cases of this condition.

**Recessive ataxia of Beauce**

This is a condition characterized by progressive problems with movement due to a loss (atrophy) of nerve cells in the cerebellum. People with this condition initially experience impaired speech (dysarthria), problems with coordination and balance (ataxia) or both. They may also have difficulty with movements that involve judging distance or scale (dysmetria). Other features include abnormal eye movements (nystagmus) and problems following the movements of objects with the eyes.

More than 100 people worldwide have been diagnosed with this condition. It is inherited in an autosomal recessive pattern.

***Causes***

Mutations in the SYNE1 gene cause autosomal recessive cerebellar ataxia Type 1. The SYNE1 gene provides instructions for making a protein called Syne-1 that is found in many tissues, but it seems to be especially critical in the brain. Within the brain, the Syne-1 protein appears to play a role in the maintenance of the cerebellum. The Syne-1 protein is active in Purkinje cells, which are located in the cerebellum and are involved in chemical signaling between nerve cells (neurons).

SYNE1 gene mutations that cause recessive ataxia of Beauce result in an abnormally short, dysfunctional version of the Syne-1 protein. The defective protein is thought to impair Purkinje cell function and disrupt signaling between neurons in the cerebellum. The loss of brain cells in the cerebellum causes the movement problems characteristic of ARCA1, but it is unclear how this cell loss is related to impaired Purkinje cell function.

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