Name:ADENUGA ADEOLA OLUWAPELUMI

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DEPARTMENT: MEDICINE AND SURGERY

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

 **Developmental genetics of the cerebellum**

The cerebellum is a pivotal centre for the integration and processing of motor and sensory information. Its extended development into the postnatal period makes this structure vulnerable to a variety of pathologies, including neoplasia. How the phenotypically distinct cell types of the cerebellum emerge rests on understanding how gene expression differences arise in a spatially and temporally coordinated manner from initially homogeneous cell populations. Tracing the developmental histories of cells in this way coupled with analysis of gene expression patterns has provided insight into the developmental genetic programmes that instruct cellular heterogeneity. A limitation to date has been the bulk analysis of cells, which blurs lineage relationships and obscures gene expression differences between cells that underpin the cellular taxonomy of the cerebellum The internal structure of the cerebellum reflects an intriguing paradox; its cytoarchitecture is relatively simple and repeated throughout, yet the connections between its neurons are wired into a complex array of gene expression domains and functional circuits. The developmental mechanisms that coordinate the establishment of cerebellar structure and circuitry provide a powerful model for understanding how functional brain networks are formed. Two primary germinal zones generate the cells that make up the cerebellum. Each zone expresses a specific set of genes that establish the cell lineages within the cerebellar anlage. Then, cohorts of differentiated projection neurons and interneuron progenitors migrate into the developing cerebellum. Thereafter, a number of remarkable patterning events occur including transformation of the smooth cerebellar surface into an intricately patterned series of folds, formation of three distinct cellular layers, and the demarcation of parasagittal gene expression domains. Together, these structural and molecular organizations are thought to support the proper connectivity between incoming afferent projections and their target cells. After birth, genetic programs and neural activity repattern synaptic connections into topographic neural networks called modules, which are organized around a longitudinal zone plan and are defined by their molecular, anatomic, and functional properties.

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. The Reelin gene through effective studying was revealed to be 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.

**Genetic bases of disorders of the cerebellum**

The list of genes that when mutated cause disruptions in cerebellar development is rapidly increasing. Improvements in brain imaging, such as magnetic resonance imaging (MRI) and the emergence of better classification schemes for human cerebellar malformations, have recently led to the identification of a number of genes which cause human cerebellar disorders. Cerebellar disorders are rare. They are often called "ataxias". According to Musselman et al (2014), the prevalence of childhood ataxia is 26/100,000 children. Ataxia is rare compared to cerebral palsy (211/100,00) and autism (620/100,000). Many cerebellar disorders are genetic in origin. In general, prevalance of genetic disorders and especially autosomal recessive disorders is much higher in populations where there is more consanguinity. Examples of this include Quebec, Canada and the Al-Kharga district in Egypt. There are also many acquired cerebellar disorders. For example, drinking too much alcohol for a long time causes a cerebellar disorder.

 Advances in brain imaging techniques and improvements in the classification of human cerebellar malformations have further aided the discovery of genes regulating cerebellar development. Genetics has recently enabled the identification of genes causing human pontocerebellar hypoplasia, Joubert syndrome, and Dandy–Walker malformation (DWM). When combined with studies in mouse, a variety of molecular mechanisms, including transcriptional regulation, mitochondrial function, and ciliary signaling have been implicated in homeostasis, patterning, and cell proliferation during cerebellar development.

 Some cerebellar disorders include:

 cerebellar vermis hypoplasia (CVH), DWM, Joubert syndrome and related disorders (JSRD), and pontocerebellar hypoplasia. Most of these diagnoses associated with intellectual and motor disabilities.

* CVH is characterized by a small hypoplastic cerebellum with the vermis more affected than the hemispheres.
* DWM includes CVH; however, there is also an upward rotation of the cerebellar vermis that results in an enlarged fourth ventricle, and an increased size of the posterior fossa. DWM is the most common cerebellar malformation, with an estimated incidence of approximately 1 in 5,000.CVH is also relatively common and often confused with DWM, making estimations of incidence problematic. CVH and DWM often present as sporadic cases, although there are several CVH loci with known recessive or X-linked inheritance .Mendelian inheritance for DWM is rare, and the genetics are likely oligogenic.
* JSRD are most often autosomal recessive disorders and are rare, with a population incidence estimated to be 1/100,000. As a group, JSRD are characterized by cerebellar vermis hypoplasia plus the presence of elongated cerebellar peduncles and a deepened interpeduncular fissure that appear as a “molar tooth” on axial brain scans. In addition, these patients exhibit axon guidance defects that include a decussation failure of the pyramidal tract and superior cerebellar peduncles. Patients with PCH exhibit a heterogeneous set of malformations characterized by hypoplasia and atrophy of the cerebellum, inferior olive, and ventral pons. This degenerative disorder often begins with embryonic atrophy of these regions.
* Pancreas specific transcription factor 1a (Ptf1a) was initially implicated as a basic helix–loop–helix transcription factor in pancreatic development since mice with a targeted deletion lacked pancreatic tissue. Further investigations determined that loss of Ptf1a causes a failure to generate GABAergic cerebellar neurons in the embryonic cerebellar anlage in both human and mouse. Since Purkinje cells, which are GABAergic, are also required for the proliferation of cerebellar granule neurons, humansl lacking Ptf1a exhibit profound cerebellar agenesis.
* Transcription factors have also been implicated in other types of cerebellar malformations. Heterozygous loss of the ZIC1 and ZIC4 genes encoding zinc finger transcription factors can cause DWM. Mutations in FOXC1, a transcription factor gene have recently been shown to contribute to human DWM. In addition to regulating skull development, Foxc1 controls mesenchymally expressed signaling molecules including Bmp2 and Bmp4.

 Additional molecules have been implicated in human cerebellar malformations, which are certain to illuminate new cerebellar developmental mechanisms. Deletions of the Rho-GAP protein encoding gene Oliogphrenin-1 (OPHN1) have been found in multiple families with X-linked CVHWhile Ophn1 is required for the stabilization of glutamatergic spines it has not been implicated in regulating earlier developmental events such as cell division.

* Mutations of another molecule with a known role in synapse development have also been seen in PCH. CASK is a calcium/calmodulin-dependant serine/threonine kinase localized to synapses via membrane-associated molecules, including Neurexin. CASK also regulates gene transcription during cell proliferation. Human studies have demonstrated that patient clinical phenotypes associated with severe congenital cerebellar malformations described here can be highly variable. Less severe cerebellar malformations have been reported in patients with non-syndromic MR Autism Spectrum Disorders, and schizophrenia.
* Evidence of Purkinje cell dysfunction in cerebella from autistic patients has been demonstrated by reduced levels of glutamate decarboxylase (GAD67), which codes for a GABA-synthesizing enzyme.In addition, levels of various gene transcripts involved in GABAergic transmission are altered in lateral cerebellar hemispheres of schizophrenic patients.

 Notably, most patients with MR, autism, and other neurodevelopmental disorders rarely undergo brain imaging. Therefore, the coincidence of these disorders with cerebellar malformation is often missed.

* Cerebellar degeneration is a process in which neurons (nerve cells) in the cerebellum - the area of the brain that controls coordination and balance - deteriorate and die. Diseases that cause cerebellar degeneration can also involve other areas of the central nervous system, including the spinal cord, medulla oblongata, cerebral cortex, and brain stem. Cerebellar degeneration may be the result of inherited genetic mutations that alter the normal production of specific proteins that are necessary for the survival of neurons.  In some cases the disease is aqauired (is non-hereditary or non-genetic).

The most characteristic symptom of cerebellar degeneration is a wide-based, unsteady, lurching walk, often accompanied by a back and forth tremor in the trunk of the body. Other symptoms may include slow, unsteady and jerky movement of the arms or legs, slowed and slurred speech, and nystagmus -- rapid, small movements of the eyes.

**Associated diseases:** Diseases that are specific to the brain, as well as diseases that occur in other parts of the body, can cause neurons to die in the cerebellum. Neurological diseases that feature cerebellar degeneration include:

1. ischemic or hemorrhagic stroke, when there is lack of blood flow or oxygen to the cerebellum
2. cerebellar cortical atrophy, multisystem atrophy, and olivopontocerebellar degeneration, progressive degenerative disorders in which cerebellar degeneration is a key feature
3. Friedreich’s ataxia, and other spinocerebellar ataxias, which are caused by inherited genetic mutations that result in ongoing loss of neurons in the cerebellum, brain stem, and spinal cord
4. transmissible spongiform encephalopathies (such as Creutzfeldt-Jakob disease) in which abnormal proteins cause inflammation in the brain, including the cerebellum
5. multiple sclerosis, in which damage to the insulating membrane (myelin) that wraps around and protects nerve cells can involve the cerebellum

Acquired diseases that can cause cerebellar degeneration include:

1. chronic alcohol abuse that leads to temporary or permanent cerebellar damage
2. paraneoplastic disorders, in which a malignancy (cancer) in other parts of the body produces substances that cause immune system cells to attack neurons in the cerebellum
* **Miller-Fisher**

This is a rare disorder related to Guillain Barre, characterized by a combination of ataxia, weakness or paralysis of the eye movements, and peripheral neuropathy. Most patients present with diplopia and eventually develop complete paralysis of their eyes. Antibodies to the ganglioside GQ1b are associated with Miller Fisher syndrome. This condition should be considered when there is a combination of diplopia, ataxia, and loss of deep tendon reflexes. The ataxia is probably due to loss of sensory input to the cerebellum. Mean time of recovery is at 10 weeks

* **Inherited cerebellar degeneration**

 There are a large number of rare but well described inherited cerebellar disorders. These generally go under the names of Freidreich's ataxia, spinocerebellar atrophy, and olivo-ponto cerebellar atrophy.

**Treatment**

There is no cure for hereditary forms of cerebellar degeneration. Treatment is usually supportive and is based on the person's symptoms.  For example, drugs may be prescribed to ease gait abnormalities. Physical therapy can strengthen muscles.  Other disorders that may contribute to the cerebellar degeneration may have treatment options that ease symptoms.

The cerebellum is part of the brain. It lies under the cerebral cortex, towards the back, behind the brainstem and above the spinal cord. The cerebellum is largely involved in "coordination". Persons whose cerebellum doesn't work well are generally clumsy and unsteady. They may look like they are drunk even when they are not.

### **Diagnosis of Cerebellar disorders**

The main clinical features of cerebellar disorders include incoordination, imbalance, and troubles with stabilizing eye movements. There are two distinguishable cerebellar syndromes -- midline and hemispheric.

Midline cerebellar syndromes are characterized by imbalance. Persons are unsteady, they are unable to stand in [Romberg](https://www.dizziness-and-balance.com/practice/Romberg%20test.html) with eyes open or closed, and are unable to well perform tandem gait. Severe midline disturbance causes "trunkal ataxia" a syndrome where a person is unable to sit on their bed without steadying themselves. Some persons have "titubation" or a bobbing motion of the head or trunk. Midline cerebellar disturbances also often affect eye movements. There may be nystagmus, ocular dysmetria and poor pursuit.

Hemispheric cerebellar syndromes are characterized by incoordination of the limbs. There may be decomposition of movement, dysmetria, and rebound. Dysdiadochokinesis is the irregular performance of rapid alternating movements. Intention tremors may be present on an attempt to touch an object. A kinetic tremor may be present in motion. The finger-to-nose and heel-to-knee tests are classic tests of hemispheric cerebellar dysfunction. While reflexes may be depressed initially with hemispheric cerebellar syndromes, this cannot be counted on. Speech may be dysarthric, scanning, or have irregular emphasis on syllables.

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