

NAME: AWOJANA ANUOLUWAPO JOSEPH

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COLLEGE/DEPARTMENT: M.H.S./ M.B.B.S.

**ASSIGNMENT TITLE: CEREBELLUM AND ITS
CONNECTIONS**

COURSE TITLE: NEUROANATOMY

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Question

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

N/B: As usual, observe every research/scholarly writing rule.

A REVIEW ON THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM

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 development of the mammalian cerebellum is orchestrated by both cell-autonomous programs and inductive environmental influences. Here, we describe the main processes of cerebellar ontogenesis, highlighting the genetic programs involved in cell fate specification and some of the better-known abnormalities associated with developmental disorders of the cerebellum. The study of mouse homologues of *Drosophila* genes has provided valuable insights into the molecular basis of cerebellar development.

The cerebellum arises from both the mesencephalic and rhombencephalic vesicles of the neural tube and develops over a relatively long period of time between early embryogenesis and late childhood. Development of the cerebellum can be described in four basic stages.

In the first stage, characterization of cerebellar territory occurs at the midbrain–hindbrain boundary. Transplantation studies in chicken and mouse have found that the isthmus organizer (IsO), a region corresponding to the midbrain–hindbrain boundary expression, is crucial for specifying midbrain and cerebellar structures. At the isthmus, restricted expression of secreted factors, such as fibroblast growth factor 8, FGF8 and Wnt1, the mammalian homolog of *Drosophila* wingless gene, as well as homeobox proteins En1 and En2 and paired box genes Pax2 and Pax5 are required for early specification of midbrain and hindbrain structures.

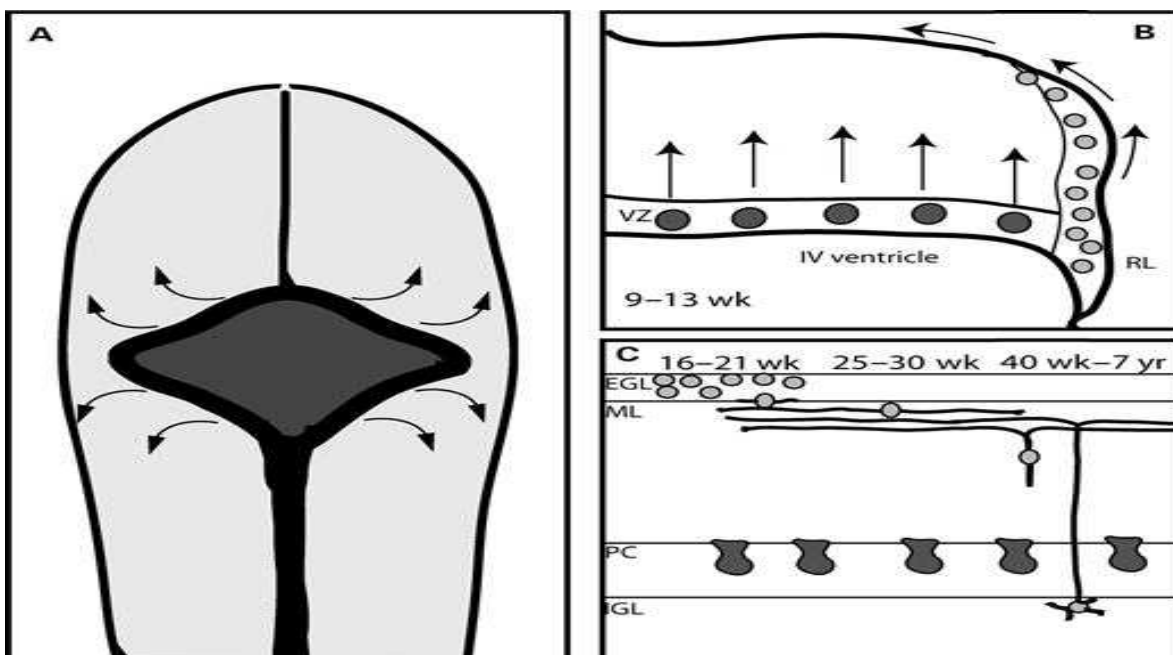
In the second stage, two compartments for cell proliferation are formed. Purkinje cells and cells of the deep cerebellar nuclei are generated in the roof of the fourth ventricle, and granule cell precursors, as well as cells of the precerebellar nuclei are formed in the rhombic lip (located between the fourth ventricle and the metencephalic roof plate). Development of Purkinje cells is not well understood, but they are known to secrete Sonic hedgehog which regulates proliferation of granule cells, by indirectly regulating the Shh pathway. By this time point, granule neuron precursors express a number of markers, Math1, nestin, zipro1/RU49 and Zic genes 1, 2 (which are thought to be involved in cell proliferation, and which requires interaction with Purkinje cells). Purkinje cells migrate radially to their final positions, whereas granule neurons migrate

over the surface of the developing cerebellum, forming the external granule layer (EGL). In the third stage, cells of the EGL migrate inward along the processes of Bergman glia to their final position in the internal granular layer (IGL).

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.

Finally, cerebellar circuitry is established and further differentiation occurs. The lower portion of the rhombic lip also gives rise to cells of the precerebellar nuclei such as the inferior olivary nuclei, which migrate to positions in the brainstem.

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.



Schematic overview of cerebellar development.

(A) Diagram of dorsal view of cerebellar anlage showing migration from the rhombic lip over the surface of the neural tube. Granule neuron precursors migrate rostrally, whereas precursors of precerebellar nuclei migrate ventrally. (B) Diagram of cross-section through the anlage showing radial migration of Purkinje cell precursors from the ventricular zone (VZ) and tangential migration of granule cells from the rhombic lip (RL). (C) 'Time-lapse' diagram of granule neuron migration. Granule cell precursors proliferate in the outer EGL. Postmitotic cells move into the inner EGL and extend parallel axons and a descending process prior to migration through the molecular layer (ML) along fibers of Bergman glia (data not shown), until settlement in the IGL. Human developmental time point indicated by wk (refers to prenatal) or yr (refers to postnatal).

GENETICS OF CEREBELLAR DISORDERS

The approach to identifying a genetic cause in patients with cerebellar disorders relies on history, examination, consultation, and testing, combined with specialized expertise because they are rare and genetically diverse. Cerebellar disorders can be caused by a variety of DNA alterations including single-nucleotide changes, small insertions or deletions, larger copy number variants, and nucleotide repeat expansions, exhibiting autosomal-recessive, autosomal-dominant (inherited and de novo), X-linked, and mitochondrial modes of inheritance. Imaging findings and a variety of neurologic and non-neurologic clinical features can help direct genetic testing and choose the most appropriate strategy. Clinical and genetic diagnoses are complementary, each providing distinct information for the care of the patient.

1). **Hereditary ataxias:** Hereditary ataxias may be autosomal recessive or autosomal dominant. Autosomal recessive ataxias include Friedreich ataxia (the most prevalent), ataxia-telangiectasia, abetalipoproteinemia, ataxia with isolated vitamin E deficiency, and cerebrotendinous xanthomatosis.

-Friedreich ataxia results from a gene mutation causing abnormal repetition of the DNA sequence GAA in the FXN gene on the long arm of chromosome 9; the FXN gene codes for the mitochondrial protein frataxin. The GAA sequence is repeated 5 to 38 times within the FXN gene in people who do not have Friedreich ataxia; however, in people with Friedreich ataxia, the GAA sequence may be repeated 70 to > 1000 times. Inheritance is autosomal recessive. Decreased frataxin levels lead to mitochondrial iron

overload and impaired mitochondrial function.

In Friedreich ataxia, gait unsteadiness begins between ages 5 and 15; it is followed by upper-extremity ataxia, dysarthria, and paresis, particularly of the lower extremities. Mental function often declines. Tremor, if present, is slight. Reflexes and vibration and position senses are lost. Talipes equinovarus (clubfoot), scoliosis, and progressive cardiomyopathy are common. By their late 20s, patients may be confined to a wheelchair. Death, often due to arrhythmia or heart failure, usually occurs by middle age.

-Spinocerebellar ataxias (SCAs) are the main autosomal dominant ataxias.

Classification of these ataxias has been revised many times recently as knowledge about genetics increases. Currently, at least 43 different gene loci are recognized; about 10 involve expanded DNA sequence repeats. Some involve a repetition of the DNA sequence CAG that codes for the amino acid glutamine, similar to that in Huntington disease.

Manifestations of SCAs vary. Some of the most common SCAs affect multiple areas in the central and peripheral nervous systems; neuropathy, pyramidal signs, and restless leg syndrome, as well as ataxia, are common. Some SCAs usually cause only cerebellar ataxia.

SCA type 3, formerly known as Machado-Joseph disease, may be the most common dominantly inherited SCA worldwide. Symptoms include ataxia, parkinsonism, and possibly dystonia, facial twitching, ophthalmoplegia, and peculiar bulging eyes.

Diagnosis

Diagnosis of cerebellar disorders is clinical and includes a thorough family history and search for acquired systemic disorders.

Neuroimaging, typically MRI, is done. Genetic testing is done if family history is suggestive.

Treatment

Some systemic disorders (eg, hypothyroidism, celiac disease) and toxin exposure can be treated; occasionally, surgery for structural lesions (tumor, hydrocephalus) is beneficial. However, treatment is usually only supportive (eg, exercises to improve balance, posture, and coordination; devices to help with walking, eating, and other daily activities).

2). **Dandy Walker Malformation (DWM)** is the most common human cerebellar malformation with an estimated incidence of 1/3000 live births. DWM is an imaging diagnosis characterized by an enlarged posterior fossa, cerebellar vermis hypoplasia, and an enlarged fourth ventricle. DWM can occur in association with agenesis of the corpus callosum, but more often occurs as an isolated finding on MRI scans. DWM clinical features are variable. Patients may exhibit symptoms ranging from intellectual disability to autism or they may be completely unaware of any deficits until diagnosed as adults for unrelated reasons. The genetic causes of DWM remain largely unknown. However, recent studies indicate that deletions in FOXC1 and ZIC1/4 are responsible for a small subset of DWM cases . Prenatal cerebellar hemorrhage however can also cause DWM, which may also be associated with genetic risk factors; however, these have yet to be determined. Research in animal models has led to the hypothesis that disruptions of posterior fossa signaling from the mesenchyme surrounding the brain to the underlying embryonic cerebellum are key. Signaling disruptions cause dramatic reductions in cerebellar anlage neuronal progenitor proliferation, as well as abnormal migration of both RL- and VZ-derived cells. This ultimately leads to foliation and lamination defects

Concluding Remarks.

The goal of this review is to provide a view of the genetic basis of cerebellar development. The broad spectrum of the work reviewed in such a short format leaves room for specific debate.

The seminal discovery of the “isthmus organizer” and its inductive role has led to an understanding of the molecular regionalization of the neural tube with its precise frontiers between domains expressing homeobox-containing genes. The interface between caudal GBX2 and rostral OTX2 expressing domains marks the location of the “isthmus organizer” which, through Fgf8 secretion, initiates the molecular cascade required for the specification of cerebellum.

Next come the germinal epithelia of the cerebellum. For over a century, the cerebellum was known for the dual origins of its neuronal populations: the VZ and the RL. Moreover, both neuroepithelia are divided into subdomains, each one specified by distinct transcription factors to generate the corresponding population of neurons.

Following specification comes neuronal migration and differentiation. Despite recent progress, the data are less complete. For example, broad areas of the early development of PCs remain obscure, even while later events such as dendritogenesis

are well understood.

Finally, the review briefly touched upon cerebellar pathology, inherited disorders of cerebellar development can now be placed in a stronger developmental context.

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