THE CEREBELLUM: DEVELOPMENTAL GENETICS AND ITS DISORDERS

OJELADE OLUWADAMILOLA

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ABSTRACT:

The cerebellum represents 10% of the brains total volume, but contains more than half of our neurons. It is one of the first brain structures to begin to differentiate, yet it is one of the last to achieve maturity- the cellular organization of the cerebellum continues to change for many months after birth. This protracted developmental process creates a special susceptibility to disruptions during embryogenesis and makes the cerebellum highly amendable to study. Over the years, genetic research has provided a great deal of information about the molecular events directing the formation of the cerebellum. Knowledge of these mechanisms help to address the nature of human diseases that have their root in developmental disorders of the cerebellum.

INTRODUCTION

The cerebellum is an important part of the central nervous system in most vertebrates. This brain structure is involved in several functions, such as motor control, reflex adaptation, motor learning and cognition . The cerebellum has 3 parts:

* Archicerebellum (vestibulocerebellum): It includes the flocculonodular lobe, which is located in the medial zone. The archicerebellum helps maintain equilibrium and coordinate eye, head, and neck movements; it is closely interconnected with the vestibular nuclei.
* Midline vermis (paleocerebellum**):** It helps coordinate trunk and leg movements. Vermis lesions result in abnormalities of stance and gait.
* Lateral hemispheres (neocerebellum**):** They control quick and finely coordinated limb movements, predominantly of the arms.

There is growing consensus that in addition to coordination, the cerebellum controls some aspects of memory, learning, and cognition.

BODY

In humans, the cerebellum develops from the dorsal region of the posterior neural tube, and its cells arise from two germinal matrices. 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. Most cells are derived from the ventricular zone, but the granule neurons come from a specialized germinal matrix called the rhombic lip. 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. The rhombic lip, located between the fourth ventricle and the metencephalic roof plate, gives rise to granule neurons. The major features of cerebellar development can be briefly summarized as follows:

* Neuronal populations are generated in a sequential manner. The inhibitory interneurons emerge from the ventricular zone and the glutamatergic neurons are generated by the rhombic lip. In mouse, the glutamatergic and gabaergic neurons in nuclei are produced first, followed by Purkinje neurons. It is established that gabaergic interneurons of the cerebellar cortex originate from a ventricular zone progenitor.
* After generation of cerebellar nuclei, the external granular layer is formed from precursors of granule cells originating from the rhombic lip. Granule cells will migrate to form the internal granular layer. It is interesting to note that these events occur at the third trimester of development in human. Survival and maintenance of Purkine neurons and granule cells is dependent on the antiapoptotic protein Lifeguard, which is highly expressed in the cerebellum and is strongly upregulated during postnatal brain development. Lifeguard antagonizes the FAS pathway. FAS receptors tune neuronal survival following trophic factors deprivation. Lifeguard affects cerebellar size, internal granular layer thickness, and Purkinje cell development, suggesting that lifeguard could participate in the pathogenesis of various human cerebellar disorders characterized by cerebellar atrophy.
* Glutamatergic unipolar brush cells migrate to the internal granular layer. Whereas the ventricular zone will lose its progenitors at late embryogenic stages, the rhombic lip remains active until postnatal period.

It is important to note that 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. 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.

GENETIC BASIS OF KNOWN CEREBELLAR DISORDERS

Cerebellar disorders have numerous causes, including congenital malformations, hereditary ataxias, and acquired conditions. Symptoms vary with the cause but typically include ataxia (impaired muscle coordination). Diagnosis is clinical and often by imaging and sometimes genetic testing. Treatment is usually supportive unless the cause is acquired and reversible.

**Congenital malformations**

Such malformations are almost always sporadic, often occurring as part of complex malformation syndromes (eg, Dandy-Walker Malformation) that affect other parts of the central nervous system (CNS).

* Dandy–Walker malformation (DWM), also known as Dandy–Walker syndrome (DWS), is a rare congenital brain malformation in which the part joining the two hemispheres of the cerebellum (the cerebellar vermis) does not fully form, and the fourth ventricle and space behind the cerebellum (the posterior fossa) are enlarged with cerebrospinal fluid. Most of those affected develop hydrocephalus within the first year of life, which can present as increasing head size, vomiting, excessive sleepiness, irritability, downward deviation of the eyes and seizures. Dandy-Walker malformation has also been associated with many chromosomal abnormalities.

This condition can be a feature of some conditions in which there is an extra copy of one chromosome in each cell (trisomy). Dandy-Walker malformation most often occurs in people with trisomy 18 (an extra copy of chromosome 18), but can also occur in people with trisomy 13, trisomy 21 or trisomy 9. This condition can also be associated with missing (delitions) or copied (duplications) pieces of certain chromosomes. Dandy-Walker malformation can also be a feature of genetic syndromes that are caused by mutations in specific genes. However, the brain malformations associated with Dandy-Walker malformation often occur as an isolated feature (not associated with other health problems), and in these cases the cause is frequently unknown.

**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 ([1](https://www.msdmanuals.com/professional/neurologic-disorders/movement-and-cerebellar-disorders/cerebellar-disorders#v48481082)). 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, ophtalmoplegia, and peculiar bulging eyes.

**Cerebellar Hypoplasia**

Cerebellar hypoplasia is characterised by a reduced cerebellar volume due to the maldevelopment of one or both hemispheres and a small but normally shaped vermis. This heterogeneous condition is associated with trisomies 9, 13 and 18, congenital disorders of glycosylation, anticonvulsant drugs (valproic acid) or cocaine.

CONCLUSION

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.

REFRENCES

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* **Hector A. Gonzalez-Usigli** ,MD, HE UMAE Centro Médico Nacional de Occidente, Cerebellar Disorders,Content last modified May 2020 msdmanuals.com
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