Name: Aliu Kudirat Oshione

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Topic: A concise review on the developmental genetics of the cerebellum highlighting the genetic bases of known cerebellar disorders.

**Abstract**

The cerebellum 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 amenable to study. Over the past few years, genetic research has provided a great deal of information about the molecular events directing the formation of the cerebellum. Knowledge of these mechanisms should enable us to address the nature of human diseases that have their root in developmental processes.

**Introduction**

The cerebellum is the second largest part of the brain located inferior to the cerebrum and posterior to the brain stem. Although the cerebellum is crucial for controlling movement, it is also implicated in higher order function such as cognition. Accordingly, its contribution to disease likely extends beyond the ataxias to include autism spectrum disorders and schizophrenia. Its potential involvement in developmental and adult onset diseases and its well-understood circuitry make the cerebellum an attractive model for investigating the mechanistic underpinnings and embryonic origins of brain circuit map formation.

Development of the Cerebellum

Soon after the cerebellar primordium is formed at the midbrain/hindbrain boundary, two primary germinal zones, the ventricular zone and the rhombic lip, sequentially generate various inhibitory and excitatory neurons, respectively. While the migration of cerebellar neurons extends well into postnatal development, work in rodents demonstrates that embryonic Purkinje cells settle into molecularly distinct parasagittal ‘clusters’, which appear to serve as a template around which circuit architecture is built. The mature circuitry of the cerebellum is organized into functional longitudinal zones. In addition to their unique circuit connectivity, Purkinje cell zones are marked by parasagittal stripes of gene and protein expression, the adult correlates of embryonic clusters. Parasagittal molecular domains are maintained even when the cerebellar surface exhibits very rapid and extensive growth along its anteroposterior axis during the stereotyped folding process called foliation. Afferent fibers arrive in the cerebellum during late embryonic and early postnatal development and terminate within specific folds in a crude map that reflects a positional code defined by Purkinje cell lineages and gene expression. Then, activity dependent mechanisms fine-tune afferent termination domains by allowing individual connections to be integrated seamlessly into longitudinal zones that can be identified by specific Purkinje cell stripes and are innervated by distinct subsets of afferent projections. The proper functioning of the cerebellum therefore requires an elaborate interplay between genetic- and activity-dependent mechanisms to guide its morphogenesis and establish its circuit connections.

Cerebellar Development from the Study of Human Cerebellar Malformation

The study of human cerebellar malformations is beginning to provide new insights regarding the basic developmental principles of the cerebellum. Currently, human patient populations with congenital developmental disorders are largely underutilized in basic research but they have proven to be valuable for identifying novel, significant developmental genes. Disruption of human cerebellar development is often severely handicapping but not lethal, making it amenable to genetic analysis. The structure of the human cerebellum facilitates the easy identification of malformations as its morphology, foliation, and lamination are stereotypical across individuals and its morphogenesis is well understood. In conjunction with advances in imaging techniques, this allows patients to be diagnosed with malformations at early post-natal or even fetal stages. While patient populations provide a great resource for researchers, they are not often employed due to several difficulties, including a lack of routine brain imaging on patients with developmental abnormalities, genetic heterogeneity among cerebellar patients resulting in the requirement of large sample sizes, and difficulties recruiting patients. Despite these obstacles, human cerebellar malformations have been used to identify cerebellar developmental genes. Gratifyingly, mutations in human RELN cause cerebellar hypoplasia, similar to the phenotype seen in the reeler mouse, demonstrating the validity of cross species comparisons. Once genes have been identified in human cerebellar malformation syndromes, mouse models have proven essential for deciphering the underlying developmental disruptions.

The Cerebellum as a Genetic System

The mature cerebellum has exquisite, stereotypical morphology, foliation, and lamination, which are consistent between individuals. 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. For example, while initial insights regarding the function of the *Reelin* gene were gleaned from studying the cerebella of *reeler* mice, recent studies have revealed that this gene is required for the emigration of dentate gyrus progenitors from a transient subpial zone and into the subgranular zone.

Genetic basics of known cerebellar Disorders

1. Ataxia- Telangiectasia: This is a rare inherited disorder that affects the nervous, immune, and other body systems. This disorder is characterized by progressive difficulty with coordinating movements (ataxia) beginning in early childhood, usually before age 5. Affected children typically develop difficulty walking, problems with balance and hand coordination, involuntary jerking movements (chorea), muscle twitches (myoclonus), and disturbances in nerve function (neuropathy), slurred speech and trouble moving their eyes to look side-to-side (oculomotor apraxia). Small clusters of enlarged blood vessels called telangiectases, which occur in the eyes and on the surface of the skin, are also characteristic of this condition.

Cause- Caused by mutations in the ATM gene. The ATM gene provides instructions for making a protein that helps control cell division and is involved in DNA repair. This protein plays an important role in the normal development and activity of several body systems. Mutations in the ATM gene reduce or eliminate the function of the ATM protein. Without this protein, cells become unstable and die. Cells in the cerebellum are particularly affected by loss of the ATM protein. Mutations in the ATM gene also prevent cells from responding correctly to DNA damage, which allows breaks in DNA strands to accumulate and can lead to the formation of cancerous tumors.

Inheritance Pattern- It is inherited in an autosomal recessive pattern, which means both copies of the ATM gene in each cell have mutations. Most often, the parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of the condition. These individuals are called carriers.

1. Joubert syndrome: It 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. Most infants with Joubert syndrome have low muscle tone in infancy, which contributes to ataxia in early childhood. Other characteristic features of the condition include episodes of unusually fast (hyperpnea) or slow (apnea) breathing in infancy, and abnormal eye movements (ocular motor apraxia). Most affected individuals have delayed development and intellectual disability. Distinctive facial features can also occur in Joubert syndrome; these include a broad forehead, arched eyebrows, droopy eyelids (ptosis ), widely spaced eyes (hypertelorism ), low set ears, and a triangle-shaped mouth. Joubert syndrome can include a broad range of additional signs and symptoms.

Cause- It 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 signaling. Primary cilia are important for the structure and function of many types of cells, including neurons and certain cells in the kidneys and liver. Primary cilia are also necessary for the perception of sensory input, which is interpreted by the brain for sight and hearing.

Joubert syndrome typically has an autosomal recessive pattern of inheritance. Rare cases are inherited in an X-linked recessive pattern. In these cases, the causative gene is located on the X chromosome,. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females.

Huntington disease: It is a progressive brain disorder that causes uncontrolled movement, emotional problems, and loss of thinking ability. Adult-onset Huntington disease, the most common form of this disorder, usually appears in a person's thirties or forties. Early signs and symptoms can include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions. Many people with Huntington disease develop involuntary jerking or twitching movements. As the disease progresses, these movements become more pronounced. Affected individuals may have trouble walking, speaking, and swallowing. A less common form of Huntington disease known as the juvenile form begins in childhood or adolescence. It also involves movement problems and mental and emotional changes.

Causes- Mutations in the HTT gene cause Huntington disease. The HTT gene provides instructions for making a protein called huntingtin. Although the function of this protein is unknown, it appears to play an important role in neurons in the brain. The HTT mutation that causes Huntington disease involves a DNA segment known as a CAG trinucleotide repeat. This segment is made up of a series of three DNA building blocks (cytosine, adenine, and guanine) that appear multiple times in a row. Normally, the CAG segment is repeated 10 to 35 times within the gene but in people with this disease, it is repeated 36 to more than 120 times. An increase in the size of the CAG segment leads to the production of an abnormally long version of the huntingtin protein. The elongated protein is cut into smaller, toxic fragments that bind together and accumulate in neurons, disrupting the normal functions of these cells. The dysfunction and eventual death of neurons in certain areas of the brain underlie the signs and symptoms of Huntington disease.

Inheritance pattern- This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. An affected person usually inherits the altered gene from one affected parent. In rare cases, an individual with Huntington disease does not have a parent with the disorder. As the altered HTT gene is passed from one generation to the next, the size of the CAG trinucleotide repeat often increases in size. People with the adult-onset form of Huntington disease typically have 40 to 50 CAG repeats in the HTT gene, while people with the juvenile form of the disorder tend to have more than 60 CAG repeats. Individuals who have 27 to 35 CAG repeats in the HTT gene do not develop Huntington disease, but they are at risk of having children who will develop the disorder. As the gene is passed from parent to child, the size of the CAG trinucleotide repeat may lengthen into the range associated with Huntington disease (36 repeats or more).

**Conclusion**

Cerebellar disorders can be caused by a variety of DNA alterations including single-nucleotide changes, small insertions or deletionslarger copy number variants and nucleotide repeat expressions, exhibiting autosomal recessive, autosomal dominant , X-linked and mitochondrial modes of inheritance.

**Reference**

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