**Name: Ekeadah adaeze c**

**Matric no: 17/ mhs01/107**

**Department: MBBS**

**Level :300**

**TOPIC: WRITE A CONCISE REVIEW ON THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM.**

**INTRODUCTION**

Talking about the developmental genetics of the cerebellum we must first understand the terminologies used to properly appreciate the topic.

* Cerebellum it lies in the posterior cranial fossa and weighs about 150g in an adult. The cerebellum plays an important role in the control of movement. It is responsible for ensuring that the movement takes places smoothly, in the right direction and to the right extent.

**NOTE: THE CEREBELLUM CONTAINS OVER HALF OF THE MATURE NEURONS IN THE ADULT BRAIN.**

* Developmental Genetics is the study of how genes control the growth and **development** of an organism throughout its life-cycle.

The developmental genetics of the cerebellum basically is talking about the genetic makeup and constitution 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 cerebella 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 cerebella 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.

There are three distinct aspects in cerebellar development, these are;

* Allocation of the cerebellar analage
* The significance of transit amplification
* The generation of neuronal diversity

**Allocation of the cerebella analage:** it is important to recognize that, beyond the stereotyped neuronal Purkinje-granule cell circuit, evolutionary variability in cerebellum form reflects variability in how these phases are deployed in the embryo. Thus, the territory that will generate the cerebellum – its ‘anlage’ – is allocated during the early embryonic segmental phase of hindbrain development close to the boundary (the ‘isthmus’) between the hindbrain and the midbrain. However, as we will describe, regulation of patterning in this earliest phase seems particularly important for the development of the uniquely mammalian midline expanded region of the cerebellum known as the ‘vermis’.

Lagging behind the establishment of rhombomere boundaries, specific cell types are allocated along the dorsoventral axis. For glutamatergic cells of the cerebellum, this is a remarkably prolonged and, importantly, a dynamic process that takes place at the most dorsal interface between neural and non-neural ‘roof plate’ tissue: the rhombic lip. This phase generates the basic dichotomy between GABAergic and glutamatergic cell types that underlies the conserved Purkinje-granule cell circuit, but, as we will see, it is also responsible for the diversity of cerebellum output connectivity across species. Cell type allocation precedes a third, distinct temporal phase of development that extends into early prenatal life. Here, the principal derivative of the rhombic lip, the granule cell precursor, accumulates over the surface of the cerebellum and undergoes further rounds of symmetric divisions in a process of transit amplification that exponentially expands its numbers.

Defining the cerebellar anlage: molecular boundaries and

the role of Fgf8

A fundamental determinant of cerebellar morphology is the

allocation of a territory in which its component cell types are

specified. Despite the distinct structure and clear boundaries of the

cerebellum, this simple problem has proved more enduring than

might have been anticipated. Similarly, the association of cerebellar

induction with the diffusible morphogen fibroblast growth factor 8

(Fgf8) has acquired a more nuanced perspective. It seems likely that

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**Defining the cerebellar anlage: molecular boundaries and the role of Fgf8**.

A fundamental determinant of cerebellar morphology is the allocation of a territory in which its component cell types are specified. Despite the distinct structure and clear boundaries of the cerebellum, this simple problem has proved more enduring than might have been anticipated. Similarly, the association of cerebellar induction with the diffusible morphogen fibroblast growth factor 8 (Fgf8) has acquired a more nuanced perspective. It seems likely that FGF signalling has far-reaching evolutionary and developmental significance for other aspects of brain development, such as the allocation of isthmic territory and the origins of the mammalian vermis, tying embryonic events at the early stages of axial specification to surprisingly profound clinical consequences for higher cognitive function.

**The cerebellar anlage sits between Hox and Otx domains**

The anlage of the cerebellum is a product of the mechanisms of segmentation that establish iterated rhombomeric subdivisions within the early hindbrain just after neural tube closure. The establishment and maintenance of the boundaries defining the territory of the cerebellum has been a subject of several recent studies. These have built our current understanding that all of the cells of the cerebellum arise from dorsal rhombomere 1 (r1), a region that is definitively characterised by an absence of the expression of Otx and Hox genes. Early studies using quail-chick grafting to map boundaries of the neuromeres of the brain concluded that the majority of the cerebellum arises from the metencephalic (rostral) hindbrain, but that as much as one-third of cerebellar granule cells originate from the mesencephalon, which is rostral to the midbrain-hindbrain constriction. Later, this idea was overturned by instead mapping the molecular boundary between the midbrain and hindbrain as the caudal extent of Otx2 expression, showing that all cerebellar cells are born from Otx2-negative tissue and also demonstrating a surprising degree of anisotropic growth proximal to the midbrain hindbrain-boundary (MHB). The caudal boundary of cerebellar territory has also been mapped by chimeric grafting to the r1/2 boundary, as marked by Hoxa2 expression.



**FGF signalling regulates territorial allocation and anisotropic cerebellar growth from rhombomere 1.** (A) In early embryonic development, the boundaries of rhombomere 1, from which the cerebellum derives, is defined by the exclusion of Otx (red) and Hox (blue) genes. FGF signalling (yellow) is established at the anterior end of rhombomere 1. (B) Colour coding indicates the contribution of territorial patterning mechanisms to regions of the adult cerebellum in birds and mammals. It seems likely that differences in their organisation reflect changes in the influence of isthmic FGF signalling on the initial expansion of the anlage. The induction of both the mammalian vermis (a medial expansion that is absent in other vertebrates) and isthmic territory, which lies just rostral to the cerebellum, is dependent on FGF (yellow). This suggests that the evolution of the mammalian vermis occurred at the expense of a more-extensive isthmic territory. Cerebellar differentiation (green) is inhibited by isthmic signalling, suggesting that FGF expands the precursor pools but is not directly involved in cerebellar specification.

**The significance of transit amplification: Transit amplification and the size and foliation of the cerebellum**: Although early events can significantly bias patterns of cerebellar growth, the final shape and size of the cerebellum is the product of a remarkable example of a discrete phase of transit amplification that occurs much later in development. This proliferative episode takes a small number of Atoh1-positive granule cell precursors and multiplies their numbers by many folds through multiple symmetrical mitoses of single fated germinal cells. The transient appearance of this population of granule cell precursors over the surface of the cerebellum was identified as a key feature of cerebellum development and offered an intuitive explanation for the massive foliation of the cerebellar surface in humans.

**NOTE: MORE RECENTLY, THE SAME LOGIC HAS MADE THE OUTERMOST LAYER OF THE CEREBELLUM, THE EXTERNAL GERMINAL LAYER, AN OBVIOUS CANDIDATE FOR MEDULLOBLASTOMA, A DEVASTATING CHILDHOOD CANCER. ALSO THE ATOH1 GENE REGULATES NEURAL DEVELOPMENT IN MULTIPLE TISSUES IN HUMANS AND ALSO IN MULTIPLE SPECIES.**

**THE GENERATION OF NEURONAL DIVERSITY; DIFFERENTIATION OF PROGENITOR ZONES AND THE GENERATION OF CELLULAR DIVERSITY:** Although the territorial allocation of the cerebellum and the expansion of granule cell numbers that shapes cerebellar morphogenesis have received a wealth of experimental scrutiny, the factors that generate cell diversity in the cerebellum have received relatively little attention. This is despite a literature that hints at important evolutionary changes in the diversity of neuronal subtypes and points to a changing functional role for the cerebellum as new networks of connections emerged in amniotes. Most recently, the importance of cerebellar connectivity as a potential locus of ASD emphasizes the need for a clear understanding of cellular specification mechanisms within cerebellar precursor pools.

***Blurred lines: GABAergic and glutamatergic progenitor domains are not lineage-restriction compartments***; In the same way as the definition of the territorial boundaries of the cerebellum was transformed by genetic insights, our understanding of the origins of different neuronal subtypes within the cerebellar anlage has been transformed in recent years. A key clarifying concept was identification of the origins of granule cell precursors at the rhombic lip, a thin strip of neuroepithelium that borders the non-neuronal roof plate of the fourth ventricle. Although it spans the entire rhombencephalon, contributing to a variety of distinct auditory, proprioceptive and interoceptive hindbrain circuits, the rhombic lip of the cerebellar anlage (rhombomere 1) is the exclusive source of granule cell precursors that then migrate tangentially to form the External Germinal Layer. The cells in the rhombic lip that contribute to the EGL already express Atoh1, which is induced by TGFβ signals secreted from the neighboring roof plate.

***Timing and diversity: how cells become specified;*** although Shh-dependent late-born populations represent the last stages of cell production in the cerebellum, a clear temporal order of cell production precedes this stage. This temporal pattern is superimposed onto dynamically maintained progenitor zones. Thus, in the rhombic lip, the production of granule cell precursors proceeds alongside that of a population of small unipolar brush cells that also express the T-box gene Tbr2 This represents the final phase in a sequence of cell specification. Granule cell precursor production is preceded by the generation of glutamatergic cerebellar nuclei, which briefly express Atoh1 but do not undergo transit amplification. The number of cerebellar nuclei varies between major amniote orders, with two in reptiles and between three and five divisions in mammals. These accumulate in a sequence with the most lateral being born first As cerebellar nuclei represent the output connection of the cerebellum, this diversity is functionally significant. For example, birds lack the most lateral of the mammalian nuclei, the Lhx9- positive dentate nucleus, which in mammals targets the thalamus. This connection allows the cerebellum to participate in regulating cortical functions and its absence in birds marks a major difference in brain organisation. Cerebellar nucleus neurons are the first cerebellar cells to be generated, but are not the earliest Atoh1 cells to be generated in rhombomere 1. At pre-cerebellar stages, the rhombic lip is patterned by FGF signalling from the isthmus and generates Lhx9-positive neurons that migrate into ventral and isthmic r1.

**2) GENETIC BASES FOR KNOWN CEREBELLAR DISORDERS**

**OUTLINE:**

1. INTRODUCTION
2. TYPES OF GENETIC BASED CEREBELLAR DEFECT
3. CAUSES OF THESE DEFECTS
4. TREATMENT AND MANAGEMENT

**INTRODUCTION**

The presence of cerebellar structural abnormalities as the predominant finding on CT scan of the brain often poses a diagnostic challenge to clinicians, because the anatomical abnormality itself is non-specific in most cases. Readily apparent conditions like Dandy–Walker syndrome, retrocerebellar cysts or trapped IVth ventricle syndrome can be recognized by neuro-imaging (CT, MRI) and have not been included in the present study. Major questions concerning the aetiology, prognosis and possibility of genetic transmission of such conditions often arise and can only (but not always) be addressed after extensive diagnostic exploration.

Here I will be trying to determine the etiology and incidence of known metabolic and hereditary disorders associated with either unilateral or bilateral structural abnormalities of the cerebellum.

**TYPES OF GENETIC CEREBELLAR DISORDERS**

There are numerous causes of cerebellar disorders, these includes;

* Congenital malformations.
* Hereditary ataxias.
* Acquired conditions

I will be focusing on the genetic cerebellar disorders;

Spinocerebellar ataxia: Is a term referring to a group of hereditary ataxias that are characterized by degenerative changes in the part of the brain related to the movement control (cerebellum), and sometimes in the spinal cord. There are many different types of SCA, and they are classified according to the mutated (altered) gene responsible for the specific type of SCA. The types are described using "SCA" followed by a number, according to their order of identification: SCA1 through SCA40 (and the number continues to grow). The signs and symptoms may vary by type but are similar, and may include an uncoordinated walk (gait), poor hand-eye coordination, and abnormal speech (dysarthria). SCA is inherited in an autosomal dominant manner. However, the term "spinocerebellar" may be found with other diseases, such as the autosomal recessive spinocerebellar ataxias (SCAR).Treatment is supportive and based on the signs and symptoms present in the person with SCA.

**NOTE: THE MOST COMMON TYPE OF SCA ARE THE SCA1, SCA2, SCA3, SCA6 AND PEOPLE AFFECTED BY THESE TYPES OF SCA USUALLY REQUIRE A WHEELCHAIR BY THE AGE OF 10-15.**

**SYMPTOMS:** There are many different types of spinocerebellar ataxia (SCA) and each may have unique signs and symptoms. However, in general, it is difficult to differentiate among the different types, and all are characterized by problems with movement that tend to get worse over time. Affected people may experience the following:

* Problems with coordination and balance (ataxia)
* Uncoordinated walk
* Poor hand-eye coordination
* Abnormal speech (dysarthria)
* Involuntary eye movement
* Vision problems
* Difficulty processing, learning, and remembering information

Depending on the type of SCA, signs and symptoms can develop anytime from childhood to late adulthood. SCA3, also known as Machado-Joseph disease, is the most common type of SCA. SCA types 9 through 36 are rare and less well characterized.

**CAUSES:** Mutations in many different genes are known to cause the different types of spinocerebellar ataxia (SCA). For some types, the gene known to cause it has been identified, while in others, the genetic cause is still unknown (about 25% to 40% of the cases).

Some types of SCA inherited in an autosomal dominant manner are caused by trinucleotide repeat expansions. A trinucleotide repeat is a segment of DNA that is repeated a number of times. It is normal for these repeats to exist and they typically do not cause any problems. However, a greater than normal number of repeats can interfere with the function of the gene, resulting in a genetic condition. Trinucleotide repeats are unstable and can change in length when passed from parent to child. An increased number of repeats often lead to an earlier age of onset and more severe disease.

 **DIAGNOSIS:** Genetic testing is available for many different genes known to cause spinocerebellar ataxia (SCA). Carrier testing for at-risk relatives and prenatal testing are possible if the disease-causing mutations in the family are known.
For some types of SCA, the genetic cause is still unknown. Genetic testing is not available for families with these types of SCA.

A diagnosis of spinocerebellar ataxia (SCA) is often suspected when certain signs and symptoms, such as a poorly coordinated gait and uncoordinated hand/finger movements, are present. Genetic testing is the best way to confirm SCA and identify the specific type, especially when a person also has family members with similar features. However, this is only an option if the disease-causing [gene](http://www.genome.gov/Glossary/index.cfm?id=70" \t "_blank) for that particular type of SCA has been identified. At this time, the genetic cause of some of the types is currently unknown; in these cases, imaging studies such as [computed tomography](http://www.nlm.nih.gov/medlineplus/ency/article/003330.htm%22%20%5Ct%20%22_blank) (CT scan) and/or magnetic resonance imaging (MRI scan) may be necessary to establish a diagnosis. Both of these imaging methods can be used to identify brain abnormalities found in people with SCA.

**TREATMENT:** There is no known cure for spinocerebellar ataxia (SCA). The best treatment options for SCA vary by type and often depend on the signs and symptoms present in each person. The most common symptom of SCA is ataxia (a condition in which coordination and balance are affected). Physical therapy can help strengthen muscles, while special devices (e.g., cane, crutches, walker, or wheelchair) can assist in mobility and other activities of daily life. Many people with SCA have other symptoms in addition to the ataxia such as tremors, stiffness, muscle spasms, and sleep disorders; medications or other therapies may be suggested for some of these symptoms.  Drugs like [zolpidem](https://www-uptodate-com.ezproxy.nihlibrary.nih.gov/contents/zolpidem-drug-information?source=see_link" \t "_blank) 10 mg has been used for patients with SCA type 2 and showed good result, while for SCA3 it was found that [varenicline](https://www-uptodate-com.ezproxy.nihlibrary.nih.gov/contents/varenicline-drug-information?source=see_link" \t "_blank) led to improvement in some, but not all of the symptoms.

**Friedreich ataxia:** This is s a rare genetic disease that causes difficulty walking, a loss of sensation in the arms and legs, and impaired speech. It’s also known as spinocerebellar degeneration and its inheritance is autosomal recessive. The disease causes damage to parts of your brain and spinal cord and can also affect your heart. “Ataxia” means lack of order. There are a number of types of ataxia with a number of causes.

Friedreich’s ataxia is one type of this condition. Friedreich’s ataxia affects approximately [1 in every 40,000 people](http://ghr.nlm.nih.gov/condition/friedreich-ataxia%22%20%5Ct%20%22_blank). Although there’s no cure for Friedreich’s ataxia, there are several treatments available to help you cope with the symptoms.

**SYMPTOMS:** Friedreich’s ataxia can be diagnosed between ages 2 to the early 50s, but its most commonly diagnosed between ages 10 to 15. Difficulty with walking is the most common initial symptom of the condition. Other symptoms include:

* vision changes
* loss of hearing
* weak muscles
* lack of reflexes in your legs
* poor coordination or lack of coordination
* speech problems
* involuntary eye movements
* foot deformities, such as clubfoot
* difficulty sensing vibrations in your legs and feet

Many people with this condition also have some form of heart disease. Approximately 75% of people with Friedreich’s ataxia have heart abnormalities. The most common type is hypertrophic cardiomyopathy, a thickening of the heart muscle. The symptoms of heart disease include heart palpitations, chest pain, and shortness of breath. Friedreich’s ataxia can eventually lead to diabetes.

**CAUSES:** Friedreich’s ataxia is a genetic defect that’s inherited from both parents by what’s called “autosomal recessive transmission.” The disease is linked to a gene called FXN. Normally this gene will cause your body to produce up to 33 copies of a specific DNA sequence. In people with Friedreich's ataxia, this sequence may repeat 66 to over 1,000 times. When production of this DNA sequence spirals out of control, severe damage to the brain’s cerebellum and the spinal cord can result.

People with a family history of Friedreich’s ataxia are at greater risk of inheriting this disease. If the defective gene is only passed down from one parent, the person becomes a carrier of the disease but usually doesn’t experience symptoms of it.

**DIAGNOSIS:** A complete history should be taken or a review of previous medical history and perform a complete physical exam. This will include a detailed neuromuscular exam. The exam will focus on checking for problems with your nervous system. The signs of damage include poor balance, lack of reflexes, and lack of sensation in your joints. A CT scan and MRI of your brain and spinal cord should be carried out. You might also have regular X-rays of your head, spine, and chest taken.

Genetic testing can show if you have the defective frataxin gene that causes Friedreich’s ataxia. An electromyography might also be ordered to measure the electrical activity in your muscle cells. A nerve conduction study may be done to see how quickly your nerves send impulses.

An eye exam should also be ordered to check your optic nerve for signs of damage. In addition, also an echocardiogram and electrocardiograms should be order to diagnose heart disease.

**TREATMENT:** Friedreich’s ataxia can’t be cured. The Doctor will treat underlying conditions and symptoms instead. Physical therapy and speech therapy can help patient function. Patient may also require walking aids to help move around. Braces and other orthopedic devices or surgery might be necessary if you develop a curved spine or problems with your feet. Medications may be used to treat heart disease and diabetes.