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**COURSE: NEURO ANATOMY**

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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.**

 **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**

During the early stages of [embryonic development](https://en.wikipedia.org/wiki/Embryogenesis), the brain starts to form in three distinct segments:

The [prosencephalon](https://en.wikipedia.org/wiki/Prosencephalon%22%20%5Co%20%22Prosencephalon),

The [mesencephalon](https://en.wikipedia.org/wiki/Mesencephalon),

And the [rhombencephalon](https://en.wikipedia.org/wiki/Rhombencephalon).

The rhombencephalon is the most caudal (toward the tail) segment of the embryonic brain; it is from this segment that the cerebellum develops. Along the embryonic rhombencephalic segment develop eight swellings, called [rhombomeres](https://en.wikipedia.org/wiki/Rhombomere%22%20%5Co%20%22Rhombomere). The cerebellum arises from two rhombomeres located in the [alar plate](https://en.wikipedia.org/wiki/Alar_plate) of the [neural tube](https://en.wikipedia.org/wiki/Neural_tube), a structure that eventually forms the brain and spinal cord. The specific rhombomeres from which the cerebellum forms are rhombomere 1 (Rh.1) caudally (near the tail) and the "isthmus" rostrally (near the front).

Two primary regions are thought to give rise to the neurons that make up the cerebellum. The first region is the ventricular zone in the roof of the [fourth ventricle](https://en.wikipedia.org/wiki/Fourth_ventricle). This area produces [Purkinje cells](https://en.wikipedia.org/wiki/Purkinje_cell) and deep cerebellar [nuclear](https://en.wikipedia.org/wiki/Nucleus_%28neuroanatomy%29) neurons. These cells are the primary output neurons of the cerebellar cortex and cerebellum. The second germinal zone (cellular birthplace) is known as the Rhombic lip, neurons then move by human embryonic week 27 to the [external granular layer](https://en.wikipedia.org/wiki/External_granular_layer_%28cerebellar_cortex%29). This layer of cells—found on the exterior of the cerebellum—produces the granule neurons. The granule neurons migrate from this exterior layer to form an inner layer known as the internal granule layer. The external granular layer ceases to exist in the mature cerebellum, leaving only granule cells in the internal granule layer. The cerebellar [white matter](https://en.wikipedia.org/wiki/White_matter) may be a third germinal zone in the cerebellum; however, its function as a germinal zone is controversial.

**THE CEREBELLUM AS A GENETIC SYSTEM**

 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. For example, while initial insights regarding the function of the Reelingene were gleaned from studying the cerebella of reelermice, 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. 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.

 In addition to spontaneous and targeted mouse mutants, 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. As in the mouse, disruption of human cerebellar development is often severely handicapping but not lethal, making it amenable to genetic analysis. Also similar to mice, 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.

**GENETIC DISORDERS OF THE CEREBELLUM**

1. **Cerebellar ataxia** is a form of [ataxia](https://en.wikipedia.org/wiki/Ataxia) originating in the [cerebellum](https://en.wikipedia.org/wiki/Cerebellum).[[1]](https://en.wikipedia.org/wiki/Cerebellar_ataxia#cite_note-1) [Non-progressive congenital ataxia](https://en.wikipedia.org/wiki/Non-progressive_congenital_ataxia) (NPCA) is a classical presentation of cerebral ataxias.

Cerebellar ataxia can occur as a result of many diseases and may present with symptoms of an inability to coordinate balance, gait, and extremity and eye movements. Lesions to the cerebellum can cause [Dyssynergia](https://en.wikipedia.org/wiki/Dyssynergia), [Dysmetria](https://en.wikipedia.org/wiki/Dysmetria%22%20%5Co%20%22Dysmetria), [Dysdiadochokinesia](https://en.wikipedia.org/wiki/Dysdiadochokinesia%22%20%5Co%20%22Dysdiadochokinesia), [Dysarthria](https://en.wikipedia.org/wiki/Dysarthria) and ataxia of stance and gait. Deficits are observed with movements on the same side of the body as the lesion (ipsilateral). Clinicians often use visual observation of people performing motor tasks in order to look for signs of ataxia.

Damage to the cerebellum causes impairment in motor skills and can cause [Nystagmus](https://en.wikipedia.org/wiki/Nystagmus%22%20%5Co%20%22Nystagmus). Almost a third of people with isolated, late onset cerebellar ataxia go on to develop [Multiple System Atrophy](https://en.wikipedia.org/wiki/Multiple_system_atrophy).

The cerebellum's role has been observed as not purely motor. It is combined with intellect, emotion and planning.

There are many causes of cerebellar ataxia including, among others, [gluten ataxia](https://en.wikipedia.org/wiki/Ataxia#Gluten_ataxia), [autoimmunity](https://en.wikipedia.org/wiki/Autoimmunity) to [Purkinje cells](https://en.wikipedia.org/wiki/Purkinje_cells) or other neural cells in the cerebellum, CNS [vasculitis](https://en.wikipedia.org/wiki/Vasculitis%22%20%5Co%20%22Vasculitis), [multiple sclerosis](https://en.wikipedia.org/wiki/Multiple_sclerosis), infection, bleeding, infarction, tumors, direct injury, toxins (e.g., alcohol), [genetic disorders](https://en.wikipedia.org/wiki/Spinocerebellar_ataxia) and [neurodegenerative diseases](https://en.wikipedia.org/wiki/Neurodegenerative_diseases) (such as [progressive supranuclear palsy](https://en.wikipedia.org/wiki/Progressive_supranuclear_palsy) and [multiple system atrophy](https://en.wikipedia.org/wiki/Multiple_system_atrophy)). Gluten ataxia accounts for 40% of all sporadic idiopathic ataxias and 15% of all ataxias.

Primary auto-immune ataxias (PACA) lack diagnostic biomarkers. Cerebellar ataxias can be classified as sporadic, autosomal recessive, X-linked, autosomal dominant and of mitochondrial origin.

1. **Joubert syndrome** 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](https://ghr.nlm.nih.gov/art/large/molar-tooth-sign.jpeg), which can be seen on brain imaging studies such as magnetic resonance imaging (MRI).

Most infants with Joubert syndrome have low muscle tone (hypotonia) in infancy, which contributes to difficulty coordinating movements (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, which can range from mild to severe. Distinctive facial features can also occur in Joubert syndrome; these include a [broad forehead](https://ghr.nlm.nih.gov/art/large/broad-forehead.jpeg), [arched eyebrows](https://ghr.nlm.nih.gov/art/large/highly-arched-eyebrows.jpeg), droopy eyelids ([ptosis](https://ghr.nlm.nih.gov/art/large/ptosis.jpeg)), widely spaced eyes ([hypertelorism](https://ghr.nlm.nih.gov/art/large/hypertelorism.jpeg%22%20%5Co%20%22Image%22%20%5Ct%20%22_blank)), low-set ears, and a triangle-shaped mouth.

Joubert syndrome 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 primary cilia. Primary cilia 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 brain cells (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, hearing, and smell.

Mutations in the genes associated with Joubert syndrome lead to problems with the structure and function of primary cilia. Defects in these cell structures can disrupt important chemical signaling pathways during development.

 Joubert syndrome typically has an [autosomal recessive pattern](https://ghr.nlm.nih.gov/art/large/autorecessive.jpeg) of inheritance, which means both copies of a gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they usually do not show signs and symptoms of the condition.

Rare cases of Joubert syndrome are inherited in an [X-linked recessive pattern](https://ghr.nlm.nih.gov/art/large/xlinkrecessive.jpeg). In these cases, the causative gene is located on the [X chromosome](https://ghr.nlm.nih.gov/chromosome/X), which is one of the two [sex chromosomes](https://ghr.nlm.nih.gov/art/large/sex-chromosomes-x-and-y.jpeg).

1. **Huntington's disease** (**HD**), also known as Huntington's chorea, is an [inherited disorder](https://en.wikipedia.org/wiki/Inherited_disorder) that [results in the death of brain cells](https://en.wikipedia.org/wiki/Neurodegeneration). The earliest symptoms are often subtle problems with mood or mental abilities. A general lack of coordination and an unsteady [gait](https://en.wikipedia.org/wiki/Gait) often follow. As the disease advances, uncoordinated, jerky body movements become more apparent. Physical abilities gradually worsen until coordinated movement becomes difficult and the person is unable to talk. Mental abilities generally decline into [dementia](https://en.wikipedia.org/wiki/Dementia). The specific symptoms vary somewhat between people. Symptoms usually begin between 30 and 50 years of age but can start at any age. The disease may develop earlier in life in each successive generation. About eight percent of cases start before the age of 20 years, and are known as juvenileHD, they typically present with symptoms more like [Parkinson's disease](https://en.wikipedia.org/wiki/Parkinson%27s_disease).

HD is typically [inherited](https://en.wikipedia.org/wiki/Genetic_disorder), although up to 10% of cases are due to a new [mutation](https://en.wikipedia.org/wiki/Mutation). The disease is caused by an [autosomal dominant](https://en.wikipedia.org/wiki/Autosomal_dominant) mutation in either of an individual's two copies of a [gene](https://en.wikipedia.org/wiki/Gene) called [huntingtin](https://en.wikipedia.org/wiki/Huntingtin%22%20%5Co%20%22Huntingtin). This means a child of an affected person typically has a 50% chance of inheriting the disease. The huntingtin gene provides the genetic information for a [protein](https://en.wikipedia.org/wiki/Protein) that is also called huntingtin.

The [*HTT* mutation](https://ghr.nlm.nih.gov/art/large/gene-mutation-that-causes-huntington-disease.jpeg) that causes Huntington disease involves a DNA segment known as a [CAG trinucleotide repeat](https://ghr.nlm.nih.gov/art/large/repeatexpansion.jpeg). 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. In people with Huntington disease, the CAG segment is repeated 36 to more than 120 times. People with 36 to 39 CAG repeats may or may not develop the signs and symptoms of Huntington disease, while people with 40 or more repeats almost always develop the disorder. An increase in the size of the CAG segment leads to the production of an abnormally long version of the huntingtin protein.

 This condition is inherited in an [autosomal dominant pattern](https://ghr.nlm.nih.gov/art/large/autodominant.jpeg), 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*](https://ghr.nlm.nih.gov/gene/HTT) gene is passed from one generation to the next, the size of the CAG trinucleotide repeat often increases in size. A larger number of repeats is usually associated with an earlier onset of signs and symptoms. This phenomenon is called [anticipation](https://ghr.nlm.nih.gov/art/large/anticipation.jpeg). 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).

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