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**ANA 303**

**THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM**

**INTRODUCTION**

**The cerebellum, which stands for “little brain”, is a structure of the central nervous system. It has an important role in motor control, with cerebellar dysfunction often presenting with motor signs. In particular, it is active in the coordination, precision and timing of movements, as well as in motor learning.**

**During embryonic development, the anterior portion of the neural tube forms three parts that give rise to the brain and associated structures:**

* **Forebrain (prosencephalon)**
* **Midbrain (mesencephalon)**
* **Hindbrain (rhombencephalon)**

**The hindbrain subsequently divides into the metencephalon (superior) and the myelencephalon (inferior). The cerebellum develops from the metencephalon division.**

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

STRUCTURE

The cerebellum of mammals and birds can be divided into a reproducible series of anteroposterior folds called lobules.

The most medial region is called the **vermis**, which is surrounded on either side by the **paravermis**. Even more laterally are the hemispheres, which in mice are each roughly the same size as the vermis. The paraflocculi and flocculi are lateral extensions of the hemispheres that extend outward and

curl toward the underside of the cerebellum. None of these anatomical divisions are present when the cerebellum first forms

The cellular makeup of the cerebellum is well understood. Each mediolateral region of the cerebellum generally contains all of the major cell types where they are organized around a repeated anatomical plan. This plan consists of a three-layered cortex that surrounds an inner core of white matter and the cerebellar nuclei1 (Figure 3).

**The Innermost layer** is called the granular layer, which is dominated by the **small granule cells** (the most numerous type of neuron in the brain), but also includes *mossy fiber terminals, Golgi cells, Lugaro cells, and unipolar brush cells (UBCs*).

**The Outermost layer** is the molecular layer, which contains *granule cell axons (parallel fibers), climbing fiber terminals, Purkinje cell dendrites, stellate cells, and basket cells*. Between these two layers is a monolayer of Purkinje cell somata thatmake up the Purkinje cell layer.

Sandwiched between the Purkinje cells are specialized glial cells called Bergmann glia, and in lower numbers candelabrumcells.

In addition to climbing and mossy fibers, a third class of afferents that have ‘beaded’ protrusions and are presumed to be neuromodulatory, terminate in all three layers of the cerebellum and within the cerebellar

nuclei

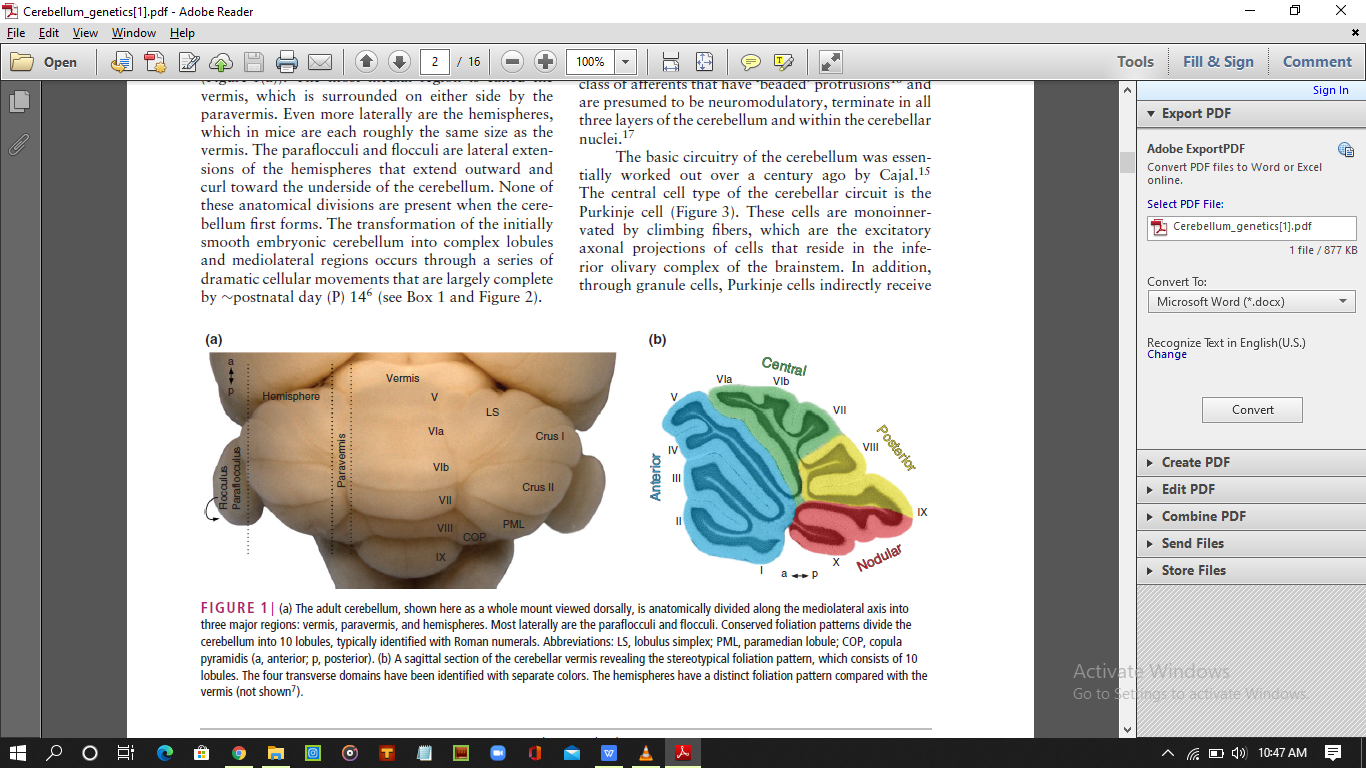
**CEREBELLAR CIRCUITRY**

**The basic circuitry of the cerebellum was essentially worked out over a century ago by Cajal.**

**The central cell type of the cerebellar circuit is the**

**Purkinje cell. These cells are monoinnervated by climbing fibers, which are the excitatory axonal projections of cells that reside in the inferior**

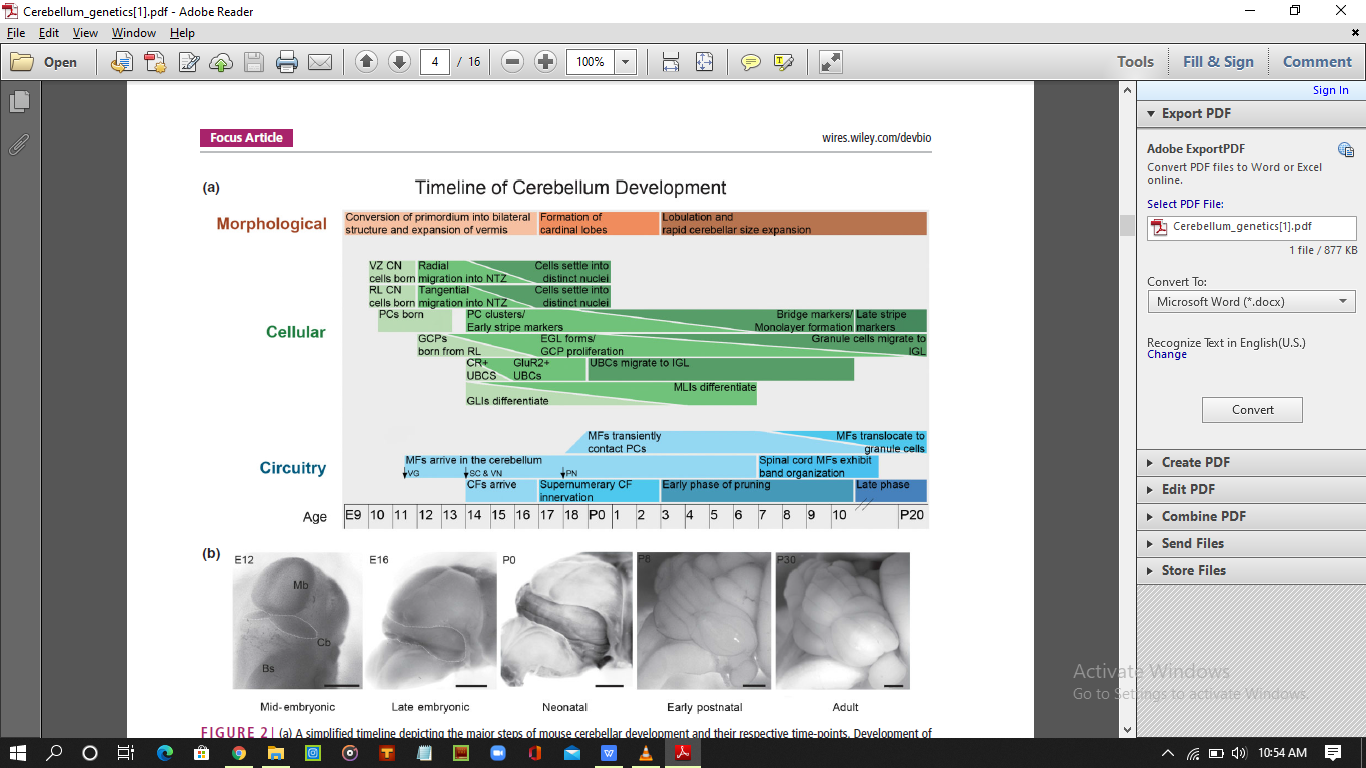
**olivary complex of the brainstem. In addition, through granule cells, Purkinje cells indirectly receive**

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**can terminate on the dendrites of about 300 Purkinje cells. These excitatory drives onto Purkinje cells are thought to be modulated by inhibition from the stellate and basket cells. By integrating excitatory**

**and inhibitory signals, Purkinje cells can appropriately respond to incoming sensory information by controlling the output of cerebellar and vestibular nuclei neurons, which ultimately communicate cerebellar**

**computations to the rest of the brain and spinal cord.**

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**Despite its relatively simple cytoarchitecture, a more complicated cerebellar organization is revealed by both the expression of molecular markers and axon termination patterns. In the adult, the antigen**

**ZebrinII, which recognizes aldolase C (ALDOC), is one of several markers that reveals a striking array of parasagittal stripes in mammalian**

**and avian Purkinje cells . Stripes do not run uninterrupted from anterior lobules to posterior lobules. Instead, there are four domains that each**

**have a unique pattern of stripes; anterior = lobules I–V; central = lobules VI–VII; posterior = lobules VIII–IX; nodular = lobules IX–X . For example, the stripes of ALDOC in lobule V are distinct from those in lobule VIII, and the two patterns are interrupted by a unique uniform domain in lobule VI.These divisions are reflected not only by gene expression patterns but also in the phenotypes of naturally occurring mutant mice, which display differential defects in the structure of the cerebellum**

**along the anteroposterior axis. In addition, each transverse domain contains a unique combination of functionally distinct afferent fibers. For instance, the spinocerebellar tract, which carries proprioceptive**

**and cutaneous information from the lower limbs and trunk, projects to lobules I–V and VIII/IX, while the vestibulocerebellar tract, which carries**

**information about balance projects mainly to lobules IX and X.**

**ESTABLISHMENT OF THE CEREBELLAR PRIMORDIUM**

**The cerebellum is derived from dorsal rhombomere 1, which comprises the most anterior aspect of the hindbrain. Expression of the homeobox genes Otx2 and Gbx2 are essential for the development of the midbrain and hindbrain. During development, these two genes are expressed in abutting domains where they antagonize each other to establish the mid/hindbrain boundary and formation of an isthmic organizer (IsO). The IsO functions as a classic signaling center by secreting fibroblast growth factor 8 (FGF8), which maintains the posterior border of Otx2 expression and is crucial for normal cerebellar development. FGF**

**expression is strongly controlled during hindbrain development and its loss results in the absence of the midbrain and cerebellum.Accordingly, FGF expression is required for cell survival and to regulate**

**gene expression in the mid/hindbrain region.**

**Different mediolateral and anteroposterior regions of the midbrain and cerebellum require varying levels and durations of FGF signaling for proper development. For instance, a slight reduction in FGF8 signaling results in a specific loss of posterior midbrain and the vermis. Moreover, the different isoforms of FGF8 that are expressed in the IsO have specific receptor affinities and their ectopic expression causes distinct developmental disruptions with mis-expression of FGF8b causing a deletion of the midbrain and gain of cerebellar territory whereas**

**FGF8a promotes an increase in midbrain tissue.**

**The ability of FGF8 to induce distinct structures depends not only on the strength of the signal but also on its duration. For example, transient Fgf8 expression between day8 and day10 is sufficient to induce**

**the formation of the lateral cerebellum but not the vermis.**

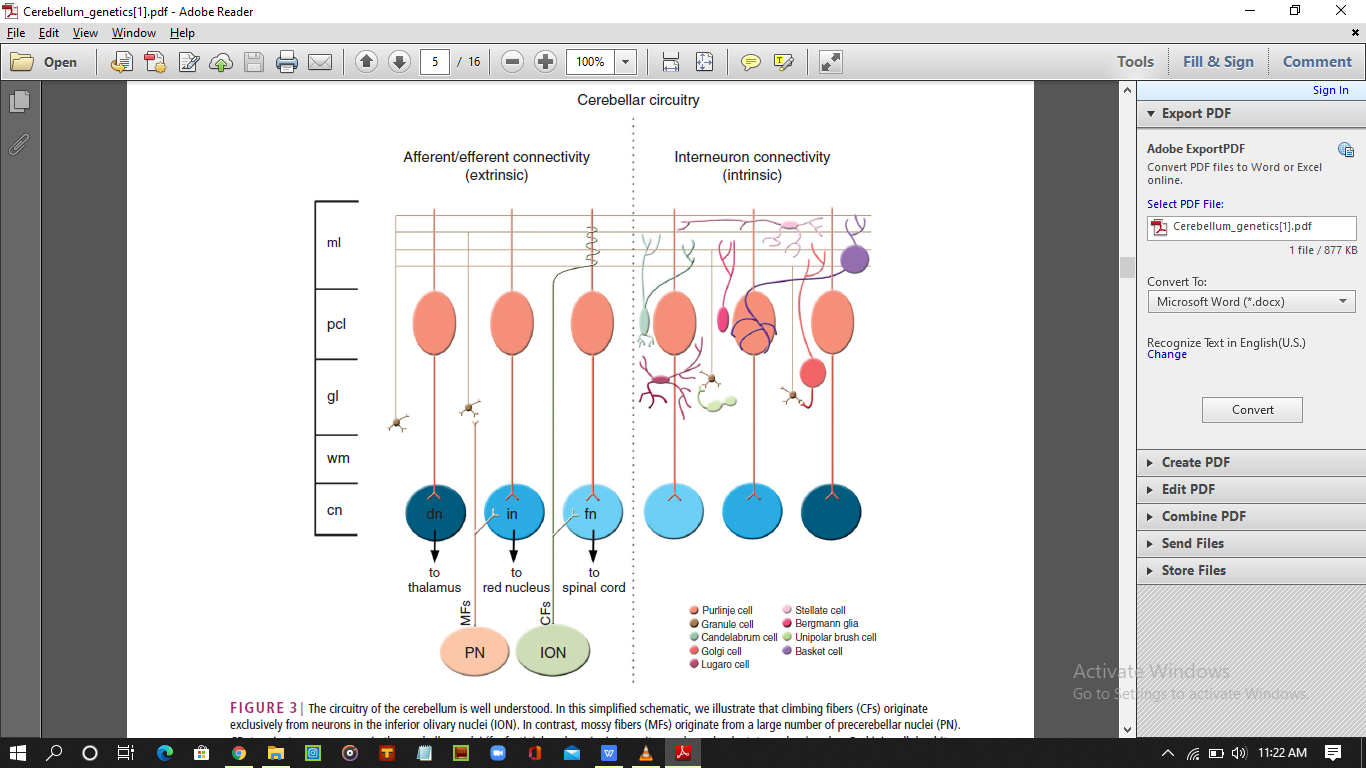
**DEVELOPMENT OF LOCAL CIRCUIT NEURONS**

**The external granular layer (EGL) is a transient structure that covers the surface of the cerebellum by day 15 in mice. The EGL is the only source of granule cells. Loss of this structure begins at ∼P0 because of the inward radial migration of post-mitotic granule cells along Bergmann glia fibers through developing Purkinje cells and into the internal granular layer.**

**Cell-cycle exit of the precursors and migration of post-mitotic granule cells require a well-orchestrated cascade of events including chemical and electrical signaling.Signals include SHH from Purkinje cells,**

**the neuropeptide somatostatin, and NMDA receptor activation by glutamate. Together, these signals converge and cause changes such as calcium influx into granule cells, and ultimately control the initiation,**

**termination, and rate of migration of granule cells. Granule cellmigration is completed by day 20 in mice, which corresponds to the final stages of foliation.**

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**Similar to granule cells, UBCs are glutamatergic, rhombic lip-derived and are contacted by mossy fibers. After these cells are born, they exit the**

**rhombic lip and migrate in the cerebellum through the developing white matter to eventually stop in the internal granular layer. In the mammalian cerebellum, UBCs are restricted primarily to the vestibulocerebellum (lobules IX/X) with an additional accumulation in**

**lobules VI/VII. They constitute an additional synapse in the indirect mossy fiber–Purkinje cell connection**

**by receiving input from mossy fibers and contacting several granule cells. Subsets of UBCs are born in different time windows and express distinct molecular markers. In rodents, UBCs are born after the cerebellar nuclei projection neurons starting at day 14 and continue to be generated in the early postnatal animal. This relatively late appearance and development hold true for the human cerebellum in which UBCs reach maturity and their ultimate density after the first year of life.**

**Golgi cells, stellate cells, and basket cells are derived from a common pool of Pax2-expressing progenitors that differentiate beginning in the embryo with the process extending into postnatal Development.**

**DEVELOPMENT AND ORGANIZATION OF CEREBELLAR STRIPED GENE**

**EXPRESSION**

**The molecular heterogeneity of Purkinje cells is obvious from day 14 in mice . However, because the expression of Purkinje cell markers is temporally dynamic and because their patterns can**

**be different at each stage, they can be divided into early markers that demarcate embryonic clusters, late markers that define adult stripes, and markers that are constitutively expressed and bridge between**

**the clusters and stripes . The temporal segregation of Purkinje cell stripe markers highlights an interesting phase during the second and third**

**weeks of life. Most well-known molecular markers either stop being expressed in stripes or begin being expressed in stripes during this period. This temporal gap in stripe patterns raised the question**

**of whether cellular and/or molecular information link early and late cerebellar patterning. Several studies have now demonstrated a lineage relationship between clusters and stripes.**

**The conclusion is that gene expression patterns in Purkinje cell clusters are repatterned into adult stripes and individual embryonic clusters seem to contribute to multiple adult stripes. However, how the cluster to stripe transformation takes place is poorly understood and the molecular signals that mediate it are not known (although reel in signaling and patterned developmental cell death of Purkinje cells**

**may be involved).**

**DEVELOPMENT OF AFFERENT TOPOGRAPHY**

**The first fibers to arrive in the developing rat cerebellum**

**are mossy fibers from the vestibular ganglion at day 13 (corresponds to day 11/12 in mouse).**

**In mice, these are followed by the vestibular nuclei and spinal**

**cord mossy fibers that arrive at Day 13/14(and Day 15 in rat) and climbing fibers at around Day 14/15. The rest of the mossy fiber projections arrive progressively during late embryonic and early postnatal development. Similarly, serotonergic ‘beaded’ fibers are first seen in the cerebellum of the rat at day 21(corresponds to Phase 0 in mouse).**

**The proper development of neural circuitry is crucial for brain function and the precision with which connections are formed depends on elaborate interactions between cell–cell communication, gene expression, and neural activity. At the time of birth, afferent fibers have a clear anteroposterior pattern but a crude mediolateral organization that is refined during postnatal development. Purkinje cells are thought to provide cues that guide afferents into specific longitudinal zones.**

**DEVELOPMENT OF EFFERENT PROJECTIONS**

**The cerebellar and vestibular nuclei are the means through which the cerebellar cortex communicates with the rest of the brain and spinal cord . Purkinje cell projections to their target cells within the cerebellar and vestibular nuclei are initiated early during Purkinje cell development. Recent studies in mouse have shown that Purkinje cell axonogenesis**

**may be initiated as early as day 12.5 and these axons have been observed in the vestibular and cerebellar nuclei by day 14.5 and day 15.5, respectively.**

**Importantly, the Purkinje cell to cerebellar nuclei projections respect the topographic organization defined by Purkinje cell molecular markers and afferent terminals**

**Together, topographically organized afferent fibers, Purkinje cell stripe gene expression, and the Purkinje cell efferent projections to the cerebellar nuclei comprise the cerebellar module, the basic**

**functional circuit of the cerebellum.**

**The cerebellum and cerebral cortex are wired together by multi-synapse networks that form closed circuit loops. The cerebellar nuclei project**

**to several major targets including the thalamus, which subsequently communicates with the cerebral cortex.The timing of when their axons**

**leave the cerebellum and contact thalamic neurons has not been determined.**

**CONCLUSION**

**Purkinje cells interact and cooperate with the other cerebellar cell types to regulate multiple developmental processes including the formation of functional topographic zones. In addition to Purkinje cell patterning,**

**the development of zonal circuits requires the proper targeting of afferent fibers settling of interneurons into specific positions, and**

**the restriction of dendrites to sagittal boundaries.**

**Not surprisingly, physical and genetic insults to the cerebellum result in a pattern of Purkinje cell death that respects the fundamental zonal architecture.**

**Cerebellar longitudinal zones comprise specific neural connections that facilitate behaviorally relevant functions. Accordingly, the synaptic activity that apparently underlies cerebellar motor learning may be**

**restricted by zonal boundaries.**

**One intriguing question about cerebellar zones is how are these complex**

**units of communication formed during development?**

**In accordance with the idea that gene function and neural activity transform embryonic patterns into a precise functional map in the adult cerebellum.**

**GENETIC BASES OF KNOWN CEREBELLAR DISORDERS.**

1. ***Huntington disease*:**

**Huntington disease is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition).**

**Signs and Symptoms: include irritability, depression, small involuntary movements,**

**poor coordination, and trouble learning new information or making decisions. Also many people with Huntington disease develop involuntary jerking or twitching movements known as chorea**

**Genetic Basis:**

**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 nerve cells (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*) thatappear 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. 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.**

1. ***Ataxia-telangiectasia:***

**Ataxia is a rare inherited disorder that affects the nervous system, immune system, 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).**

**Genetic Basis:**

**Mutations in the ATM gene cause ataxiatelangiectasia.**

**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, including the nervous**

**system and immune system. The ATM protein assists cells in recognizing damaged**

**or broken DNA strands and coordinates DNA repair by activating enzymes that Qx the**

**broken strands. Efficient repair of damaged DNA strands helps maintain the stability of**

**the cell's genetic information.**

**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 part of the brain involved in coordinating movements (the cerebellum ) are particularly affected by**

**loss of the ATM protein. The loss of these brain cells causes some of the movement**

**problems characteristic of ataxiatelangiectasia.**

**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.**

1. ***Jouberts Syndrome***

**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 , 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. The molar tooth sign got its name because the characteristic brain abnormalities resemble the crosssection of a molar tooth when seen on an MRI.**

**Signs and Symptoms:**

**Joubert syndrome can include a broad range of additional signs and symptoms. The**

**condition is sometimes associated with other eye abnormalities (such as retinal**

**dystrophy, which can cause vision loss, and coloboma, which is a gap or split in a**

**structure of the eye), kidney disease (including polycystic kidney disease and**

**nephronophthisis), liver disease, skeletal abnormalities (such as the presence of extra**

**Gngers and toes), or hormone (endocrine) problems. A combination of the**

**characteristic features of Joubert syndrome and one or more of these additional signs**

**and symptoms once characterized several separate disorders. Together, those**

**disorders were referred to as Joubert syndrome and related disorders (JSRD).**

**Now, however, any instances that involve the molar tooth sign, including those with these additional signs and symptoms, are usually considered Joubert syndrome.**

**Genetic Basis**

**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 structures called primary cilia. Primary cilia are microscopic, Gnger-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 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.**

**Defects in these cell structures can disrupt important chemical signaling pathways**

**during development.**

**Mutations in the genes known to be associated with Joubert syndrome account**

**for about 60 to 90 percent of all cases of this condition. In the remaining cases, the**

**genetic cause is unknown.**

**References:**

1. **WIRES Developmental Biology** wires.wiley.com/devbio
2. <https://teachmeanatomy.info/neuroanatomy/structures/cerebellum/>
3. https://www.nih.gov