**NAME: NWOKPOR NNAEMEKA COLLINS**

**MATRIC NUMBER: 17/MHS01/211**

**MEDICINE AND SURGERY**

**ASSIGNMENT**

**Write a concise review on the developmental genetics of the cerebellum and highlight the genetic bases of known cerebellar disorders**

The cerebellum represents 10% of the brain's total volume, but contains more than half of the neurons. It acts as a coordination centre, using sensory inputs from the periphery to fine-tune movement and balance. It is one of the first structures in the brain to begin to differentiate, but one of the last to mature, and its cellular organization continues to change for many months after birth.The cerebellum develops from the dorsal region of the posterior neural tube, and its cells arise from two germinal matrices. Most cells are derived from the ventricular zone, but the granule neurons come from a specialized germinal matrix called the rhombic lip

The mesencephalon and metencephalon both contribute to the developing cerebellum. The patterning of these two regions depends on signals from the isthmus organizer (IO), located just caudal to their junction. *Otx2* and *Gbx2* genes are central to IO development. *Otx2* gene is expressed in the mesencephalon, with a posterior boundary at the rostral metencephalon; *Gbx2* gene is expressed in the metencephalon, and its anterior boundary abuts the *Otx2* gene boundary. Reciprocal repression maintains a sharp boundary between these domains. *Otx2* and *Gbx2* genes form part of a regulatory loop that includes *Wnt1*, *En1* and *Fgf8* genes. Many other genes, including members of the Pax and Hox families, are also involved in patterning this region.

Purkinje cells, Golgi neurons, stellate and basket cells all arise from the ventricular neuroepithelium. Purkinje cells are born around embryonic day 13, and they migrate along radial glial fibres into the cerebellar anlage. During their final maturation phase, Purkinje cells develop extensive dendritic arbors and synapse onto granule neurons. This depends on granule neuron signals, probably including *Wnt3* gene. Various growth factors are required for Purkinje cells survival, including nerve growth factor, acetylcholine, neurotrophin 4/5, brain-derived neurotrophic factor and ciliary neurotrophic factor.

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. Rhombic lip cells migrate to the cerebellar anlage and settle on its periphery to form the external granule layer, another zone of proliferation. As the cells begin to migrate, they express markers that include *RU49/Zipro1*, *Zic1* and *Zic3*. *RU49/Zipro1* and *Zic1* are thought to be involved in cell proliferation, which requires interaction with Purkinje cells. Purkinje cells might release a diffusible factor such as sonic hedgehog (Shh), and *Zic1* could control cell proliferation by indirectly regulating the S*hh* pathway. The final stage of granule neuron maturation occurs after precursor cell migration into the inner granule layer. 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*gene 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. Spatial- and temporal-specific knockout strategies should yield more information about the roles of these genes in patterning the cerebellum.

Cerebellar Cells

These drawings of cerebellar cells were based upon electron micrograph images from the rat cerebellum.

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granule cell

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Bergmann astrocyte

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oligodendrocyte

Purkinje Cell

**Search:** [*Purkinje cell Development*](http://www.ncbi.nlm.nih.gov/pubmed/?term=Purkinje+cell+Development)

Historic Description

Gray H. [**Anatomy of the human body**](https://embryology.med.unsw.edu.au/embryology/index.php/Anatomy_of_the_Human_Body_by_Henry_Gray). (1918) Philadelphia: Lea & Febiger.

"The cerebellum is developed in the roof of the anterior part of the hind-brain (Figs. 649 to 654). The alar laminæ of this region become thickened to form two lateral plates which soon fuse in the middle line and produce a thick lamina which roofs in the upper part of the cavity of the hind-brain vesicle; this constitutes the rudiment of the cerebellum, the outer surface of which is originally smooth and convex. The fissures of the cerebellum appear first in the vermis and floccular region, and traces of them are found during the third month; the fissures on the cerebellar hemispheres do not appear until the fifth month. The primitive fissures are not developed in the order of their relative size in the adult—thus the horizontal sulcus in the fifth month is merely a shallow groove. The best marked of the early fissures are: (a) the fissura prima between the developing culmen and declive, and (b) the fissura secunda between the future pyramid and uvula. The flocculus and nodule are developed from the rhombic lip, and are therefore recognizable as separate portions before any of the other cerebellar lobules. The groove produced by the bending over of the rhombic lip is here known as the floccular fissure; when the two lateral walls fuse, the right and left floccular fissures join in the middle line and their central part becomes the post-nodular fissure."



Transverse section of a cerebellar folium. ([Cajal](https://embryology.med.unsw.edu.au/embryology/index.php/Embryology_History_-_Santiago_Ram%C3%B3n_y_Cajal%22%20%5Co%20%22Embryology%20History%20-%20Santiago%20Ram%C3%B3n%20y%20Cajal))

Researcher timeline based on a recent review on cerebellum[[24]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development%22%20%5Cl%20%22cite_note-PMID29903448-24)

* Rolando - role in movement control
* Flourens - role in movement coordination
* Purkinje (1837) - histology of the cerebellar cortex
* Luciani (1891) - cerebellum has a tonic facilitating effect on central structures
* Bolk (1906) - localization for coordinating action on the motor system (medio-lateral organization)
* [Cajal](https://embryology.med.unsw.edu.au/embryology/index.php/Embryology_History_-_Santiago_Ram%C3%B3n_y_Cajal) - histology of cortex circuitry
* Eccles and Ito - inhibitory interneurons and the Purkinje cells, excitatory connections of mossy and climbing afferents and granule cells
* Babinski and Holmes - anatomoclinical insights
* [Marr](https://www.ncbi.nlm.nih.gov/pubmed/?term=Marr%20D%5BAuthor%5D&cauthor=true&cauthor_uid=5452810) and Albus - theories involving cognition and emotion
* Leiners and Dow
* [Magnus](https://www.ncbi.nlm.nih.gov/pubmed?term=(Magnus%5BAuthor%5D)%20AND%20cerebellum) - cerebellum no role in body posture

Precerebellar Neurons

Precerebellar neurons (PCNs) are born in the hindbrain alar plate in the specific region called the rhombic lip (for review see[[25]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development%22%20%5Cl%20%22cite_note-PMID16111554-25)). From there they migrate by a process termed nucleokinesis[[26]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development%22%20%5Cl%20%22cite_note-PMID15882636-26), extending a cytoplasmic process then move their nucleus.

In recent years a number of different chemotactic positive and negative factors have been suggested to have a role in driving the guided migration of these cells. Many signals are thought to be mediated through the Rho family GTPases links to the cytoskeleton.

* netrin-1[[27]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development#cite_note-PMID18801355-27)
* Slit
* Nr-CAM
* Calm1 signaling pathway[[18]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development#cite_note-PMID25519244-18)

Cerebellar Nuclei

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| **Cerebellar Nuclei** |
| **Nucleus/Nuclei** | **Location** | **Function** |
| **Fastigial Nucleus** | Most medially located of the cerebellar nuclei. | Receives input from the vermis and cerebellar afferents that carry vestibular, proximal somatosensory, auditory and visual information. |
| **Interposed Nuclei** | Consists of emboliform nucleus and globose nucleus. Interposed nuclei are situated laterally with respect to the fastigial nucleus. | Receives input from intermediate zone and cerebellar afferents that carry spinal, proximal somatosensory, auditory and visual information. |
| **Dentate Nucleus** | Largest of the cerebellar nuclei. Lateral to interposed nuclei. | Receives input from lateral hemisphere and cerebellar afferents that carry information from cerebral cortex. |
| **Vestibular Nuclei** | Located outside cerebellum in the medulla. | Considered to be cerebellar nuclei as their connectivity patterns are identical to those of cerebellar nuclei. Receive input from flocculonodular lobe and from the vestibular labyrinth. |
| **Links:** cerebellum |  |  |

Cerebellar Pathways

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| Mouse cerebellum connections 01.jpg | (A) Regions that send input to the cerebellum.**Abbreviations:** AMG, amygdala; BG, basal ganglia; ECN, external cuneate nucleus; HIP, hippocampus; HYP; hypothalamus; IO, inferior olive; LC, locus coeruleus; PAG, periaqueductal gray; PN, pontine nuclei; RET, reticular nucleus; RN, red nucleus; SC, spinal cord; SUP, superior colliculi; TH, thalamus; VN, vestibular nuclei.(B) Regions that receive information from the cerebellum. Note that the TH is a major relay station for cerebellar input to the cortex while the PN is the primary gateway for cerebral cortical input to the cerebellum. |
| Cerebellum connections to the brain and spinal cord (mouse).[[28]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development#cite_note-PMID24294192-28) |  |

Molecular

* **Calm1** - signaling pathway is essential for the migration of mouse precerebellar neurons.[[18]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development#cite_note-PMID25519244-18)
* **Merlin** - impacts on cerebellar pre- and post-synaptic terminal organisation, not the overall cerebellar development.[[29]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development#cite_note-PMID31165301-29)
* [**sonic hedgehog**](https://embryology.med.unsw.edu.au/embryology/index.php/Developmental_Signals_-_Sonic_hedgehog) - signaling by Bergmann glia is required for proper cerebellar cortical expansion and architecture.[[15]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development#cite_note-PMID29792854-15)

Abnormalities

Dandy-Walker Syndrome

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| Dandy-Walker Syndrome/Malformation (DWS) is a cerebellar hypoplasia and upward rotation of the cerebellar vermis with ventricular enlargement (cystic dilation of the fourth ventricle). Named in 1954 after the earlier identification by Walter **Dandy** (1914) and Arthur Earl **Walker** (1942), two USA neurosurgeons.Walter Dandy (1886 – 1946) Arthur Earl Walker (1907 – 1995).[International Classification of Diseases](https://embryology.med.unsw.edu.au/embryology/index.php/International_Classification_of_Diseases) [Q03 Congenital hydrocephalus](https://embryology.med.unsw.edu.au/embryology/index.php/Abnormal_Development_-_Congenital_Hydrocephalus) Incl.: hydrocephalus in newborn Excl.: Arnold-Chiari syndrome (Q07.0) hydrocephalus: acquired (G91.-) due to congenital toxoplasmosis (P37.1) with spina bifida (Q05.0-Q05.4)* Q03.0 Malformations of aqueduct of Sylvius Aqueduct of Sylvius: anomaly obstruction, congenital stenosis
* Q03.1 Atresia of foramina of Magendie and Luschka Dandy-Walker syndrome

**Links:** [MP4 movie](https://embryology.med.unsw.edu.au/embryology/images/8/8c/US_Dandy-Walker_01.mp4) | [Neural Abnormalities](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_System_-_Abnormalities) | Cerebellum Development | [Ultrasound](https://embryology.med.unsw.edu.au/embryology/index.php/Ultrasound) | [OMIM - Dandy-Walker Syndrome](http://www.omim.org/entry/220200) | [Movies](https://embryology.med.unsw.edu.au/embryology/index.php/Movies) |

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| --- |
| US Dandy-Walker 01.jpg |
|  ‎‎**Dandy-Walker** |
| [Page](https://embryology.med.unsw.edu.au/embryology/index.php/Ultrasound_-_Dandy-Walker_Movie_1) | [Play](https://embryology.med.unsw.edu.au/embryology/images/8/8c/US_Dandy-Walker_01.mp4) |

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Foliation Defects



Mouse Cerebellar Foliation Defects[[30]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development%22%20%5Cl%20%22cite_note-PMID21437245-30)

(A–B) Midsagittal sections of newborn (P0) wild-type and Mdm2puro/Δ7-9 cerebella stained with H&E. (C–D) Superimposition of P0 (purple outline), P7 (blue outline), and adult (green outline) cerebella from wild-type (C) or Mdm2puro/Δ7-9 (D) mice. By P7, all four primary fissures, as well as two additional fissures, are evident in Mdm2puro/Δ7-9 mice. Moreover, even in adulthood, the mutant cerebellum does not reach the size or complexity of the wild-type cerebellum. Abbreviations are: prc, precentral; pc, pre-culminate; pr, primary; pp, prepyramidal; sec, secondary; pl, posterolateral fissures.

Joubert Syndrome

Joubert syndrome (Joubert-Boltshauser syndrome, Cerebelloparenchymal disorder 4, Cerebellar vermis agenesis) is a rare disease of the cerebellum. Identified as a ciliopathy, characterized by the absence or underdevelopment of the cerebellar vermis, that controls balance and coordination. There is also malformation of the stem, connecting the brain and spinal cord. A recent super-resolution microscopy study has shown that the syndrome is caused by disruption of the ciliary transition-zone architecture. [[31]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development#cite_note-PMID28846093-31) Ciliopathies are a class of cell abnormalities that can be caused by mutations in components of the cellular transition zone, a domain near the base of the cilium, that controls the protein composition of its membrane.

* hypotonia - weak muscle tone
* ataxia - difficulty coordinating movements
* hyperpnea - episodes of fast breathing (improves with age and usually disappears around 6 months of age)
* oculomotor apraxia - difficulty moving the eyes from side to side.
* language and motor skills
* mild to severe intellectual disability
* distinctive facial features - broad forehead, arched eyebrows, droopy eyelids (ptosis), widely spaced eyes, low-set ears, and a triangular-shaped mouth.

**Links:** [NIH - Rare Diseases](https://rarediseases.info.nih.gov/diseases/6802/joubert-syndrome)

Pontocerebellar Hypoplasia



Pontocerebellar Hypoplasia (MRI)[[32]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development%22%20%5Cl%20%22cite_note-PMID21749694-32)

Pontocerebellar Hypoplasia (PCH) are very rare, inherited progressive neurodegenerative disorders with prenatal onset (for recent review see[[32]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development%22%20%5Cl%20%22cite_note-PMID21749694-32)). The major features are: hypoplasia or atrophy of cerebellum and pons, progressive microcephaly, and variable cerebral involvement. There is a further classification of 7 different subtypes (PCH1-7) and there is prenatal testing for the related inherited mutations.

* **PCH2, PCH4, PCH5** - Mutations in the 3 tRNA splicing endonuclease subunit genes.
* **PCH6** - Mutations in the nuclear encoded mitochondrial arginyl- tRNA synthetase gene.
* **PCH1** - Mutations in the tRNA splicing endonuclease, the mitochondrial arginyl- tRNA synthetase and the vaccinia related kinase1.

Medulloblastoma

Medulloblastomas are the most common childhood primary central nervous system tumour. They are thought to arise in the developing cerebellum from the precursors of the granule cell.

Rhombencephalosynapsis

Rhombencephalosynapsis (RES) is a unique cerebellar malformation characterized by fusion of the cerebellar hemispheres with partial or complete absence of a recognizable cerebellar vermis.[[33]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development#cite_note-PMID30580482-33)

* craniofacial features - prominent forehead, flat midface, hypertelorism, ear abnormalities
* somatic malformations - [heart](https://embryology.med.unsw.edu.au/embryology/index.php/Cardiovascular_System_-_Heart_Development), [kidney](https://embryology.med.unsw.edu.au/embryology/index.php/Renal_System_Development), spine, and [limb](https://embryology.med.unsw.edu.au/embryology/index.php/Musculoskeletal_System_-_Limb_Development) defects.

Brain Function

A recent consensus paper on experimental neurostimulation of the cerebellum suggests that this may be a target for symptomatic alleviation a number of neurological conditions.[[34]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development#cite_note-PMID31165428-34) These neurological and neuropsychiatric conditions include:ataxia, dystonia, essential tremor, Parkinson's disease (PD), epilepsy, stroke, multiple sclerosis, autism spectrum disorders, dyslexia, attention deficit hyperactivity disorder (ADHD), and schizophrenia.

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