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NEUROANATOMY ASSIGNMENT

DEVELOPMENTAL GENETICS OF THE CEREBELLUM

The cerebellum represents 10% of the brain's total volume, but contains more than half of our neurons. It acts as a coordination centre, using sensory inputs from the periphery to fine-tune our 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 study of mouse homologues of *Drosophila* genes has provided valuable insights into the molecular basis of cerebellar development.

* In humans, 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 mouse cerebellum. The patterning of these two regions depends on signals from the isthmus organizer (IO), located just caudal to their junction. *Otx2* and *Gbx2* are central to IO development. *Otx2* is expressed in the mesencephalon, with a posterior boundary at the rostral metencephalon; *Gbx2* is expressed in the metencephalon, and its anterior boundary abuts the *Otx2* boundary. Reciprocal repression maintains a sharp boundary between these domains. *Otx2* and *Gbx2* form part of a regulatory loop that includes *Wnt1*, *En1* and *Fgf8*. Many other genes, including members of the Pax and Hox families, are also involved in patterning this region.
* Purkinje cells (PCs), Golgi neurons, stellate and basket cells all arise from the ventricular neuroepithelium. PCs are born around embryonic day 13, and they migrate along radial glial fibres into the cerebellar anlage. During their final maturation phase, PCs develop extensive dendritic arbors and synapse onto granule neurons. This depends on granule neuron signals, probably including *Wnt3*. Various growth factors are required for PC 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 PCs. PCs 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* 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.

GENETIC BASIS OF CEREBELLAR DISORDERS

* 1. Cerebellar degeneration is associated with a variety of inherited and non-inherited conditions. One example of an inherited form of cerebellar degeneration is [**spinocerebellar ataxia**](http://rarediseases.info.nih.gov/gard/10748/spinocerebellar-ataxia/resources/1)(SCA), which refers to a group of conditions characterized by degenerative changes of the cerebellum, brain stem, and spinal cord. Depending on the type, SCA can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner.[[3]](https://rarediseases.info.nih.gov/diseases/6019/cerebellar-degeneration#ref_7951)[[1]](https://rarediseases.info.nih.gov/diseases/6019/cerebellar-degeneration#ref_7995)  
       
     Other complex conditions such as [multiple sclerosis](http://rarediseases.info.nih.gov/gard/10255/multiple-sclerosis/resources/1) and [multisystem atrophy](http://www.nlm.nih.gov/medlineplus/ency/article/000757.htm) are also associated with cerebellar degeneration. These conditions are likely caused by the interaction of multiple genetic and environmental factors. Although complex conditions are not passed directly from parent to child, reports of familial forms exist. This suggests that a [genetic susceptibility](https://ghr.nlm.nih.gov/primer/mutationsanddisorders/predisposition) to these conditions can run in families.   
       
     Many causes of cerebellar degeneration are acquired (non-genetic and non-inherited) including strokes, [transmissible spongiform encephalopathies](https://www.ninds.nih.gov/Disorders/All-Disorders/Transmissible-Spongiform-Encephalopathies-Information-Page), chronic alcohol abuse and [paraneoplastic disorders](http://rarediseases.info.nih.gov/gard/9415/paraneoplastic-neurologic-disorders/resources/1).
  2. Cerebellar hypoplasia is a neurological condition in which the cerebellum is smaller than usual or not completely developed.  Cerebellar hypoplasia is a feature of a number of congenital (present at birth) malformation syndromes, such as Walker-Warburg syndrome (a form of muscular dystrophy. It is also associated with several inherited metabolic disorders, such as Williams syndrome, and some of the neurodegenerative disorders that begin in early childhood, such as ataxia telangiectasia.
  3. Dyssynergia Cerebellaris Myoclonica refers to a collection of rare, degenerative, neurological disorders characterized by epilepsy, cognitive impairment, myoclonus, and progressive ataxia.  Symptoms include seizures, tremor, and reduced muscle coordination.  Onset of the disorder generally occurs in early adulthood.  Tremor may begin in one extremity and later spread to involve the entire voluntary muscular system.  Arms are usually more affected than legs.  Some of the cases are due to mitochondrial abnormalities.
  4. Olivopontocerebellar atrophy (OPCA) is a term that describes the degeneration of neurons in specific areas of the brain – the cerebellum, pons, and inferior olives.  OPCA is present in several neurodegenerative syndromes, including inherited and non-inherited forms of ataxia (such as the hereditary spinocerebellar ataxia known as Machado-Joseph disease) and multiple system atrophy (MSA), with which it is primarily associated: [Multiple System Atrophy Information Page](https://www.ninds.nih.gov/Disorders/All-Disorders/Multiple-System-Atrophy-Information-Page)

OPCA  may also be found in the brains of individuals with prion disorders and inherited metabolic diseases.  The characteristic areas of brain damage that indicate OPCA can be seen by imaging the brain using CT scans or MRI studies.

REFERENCE : <https://www.nature.com/articles/35081558>

<https://medlineplus.gov/cerebellardisorders.html>