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**OVERVIEW OF HUMAN CEREBELLAR DEVELOPMENT**

The cerebellum develops from the dorsal region of the posterior neural tube. The embryonic cerebellum begins as little more than symmetric bulges into the early fourth ventricle: cerebellar hemispheres arise as mere buds from laminae on either side of the rhombencephalic midline, and the most rostral segment of the metencephalon produces outgrowths that form the first elements of the cerebellum. These lateral elements develop towards the midline and fuse in a rostral-to caudal direction. As the primitive hemispheres come into contact with each other, they form first the superior and then the inferior vermis. The lateral elements from this fusion develop into the cerebellar hemispheres. Cells in the cerebellum arise from two different germinal matrices. From the ventricular zone (also known as the ventricular germinal matrix), cells radiate laterally and evolve into the deep cerebellar nuclei and Purkinje cells of the cerebellar cortex. The first cells to be born become the deep cerebellar nuclei at about week eight in human embryogenesis. At week nine, the ventricular zone begins to produce cells that will eventually form the Purkinje neurons. By 24 weeks, these proto-Purkinje cells send dendrites to the PARALLEL FIBRES of the granule neurons. The full number of Purkinje cells is present early on, but their mature monolayer forms sometime between 16 and 28 weeks postnatally. Purkinje cells continue their maturation after birth, projecting to the deep cerebellar nuclei and refining the input they receive from the CLIMBING FIBRES of inferior olivary neurons. From the ventricular zone, a third population of neurons is born after the formation of Purkinje cells. These neurons include the stellate, basket and Golgi interneurons that can be found in the molecular layer. These three kinds of neurons have a modulatory action on the Purkinje cells and granule neurons. Unlike most of the cell types of the cerebellum, which are born at the ventricular zone, cerebellar granule neurons come from a specialized germinal matrix called the rhombic lip. Migration of these primitive cells over the surface of the cerebellum starts as early as week 11 in humans; neuronal elements are present in the external granular layer (EGL) by week 27. From the EGL, a second zone of proliferation, the granule neuron precursors, migrate deeper into the cortex. This inward migration continues after birth, with the EGL disappearing within the first year of life in humans. In the past decade, genetic studies of various mouse mutants became the primary source of information about cerebellar development. The rest of the review will focus on what is known about the development of the mouse cerebellum, highlighting some of the important genes and signaling pathways involved.

**GENES INVOLVED IN VARIOUDS STAGES OF CEREBLLAR DEVELOPMENT.**

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| S/N | STAGES/AREAS OF DEVELOPMENT | GENES, PROTEINS AND MOLECULES |
| 1 | Cerebellar primordium | Otx2, Gbx2, Fgf8, Wnt1, En1/2, Pax2/5, Bmps, Shh, Hoxa2 |
| 2 | Granule cell generation | Math1, RU49/Zipro1, Zic1,2,3, Shh pathway, Ccnd2, p27, Neurod1, NSCL1 |
| 3 | Granule cell migration | Tag1, Tuj1, Pax6, Dcc/netrin pathway, Unc5h2,3 GIRK2, astrotactin, thrombospondin, tenascin, neuregulin |
| 4 | Purkinje cell maintenance | Ngf, BDNF, ciliary neurotrophic factor, acetylcholine, Nt4/5, Rorα |
| 5 | Purkinje cell migration | Reelin pathway |

**Genes in the developing cerebellar primordium:** The neural tube can be thought of as comprising four different regions during early development. The most anterior portion of the neural tube, the prosencephalon, gives rise to the forebrain. The mesencephalon, just caudal to the prosencephalon, gives rise to the midbrain, whereas hindbrain regions evolve from the metencephalon and myelencephalon. The proper patterning of the mesencephalon and the metencephalon is dependent on molecular signals released from the ISTHMUS organizer (IO), which is located just caudal to the junction of these two regions. Morphologically, this region is marked by a sharp bend of the neural tube. It has been shown in various mouse mutants, as well as in transplant experiments, that the IO is necessary and sufficient for patterning the mid-/ hindbrain region from the neural tube. The IO is, in turn, set up by the expression of a complex array of genes. Two, in particular, are central to its development: Otx2, one of the mouse homologues of the Drosophila gene orthodenticle, and Gbx2, a homologue of the Drosophila gene unplugged. At embryonic day, Otx2 is expressed in the mesencephalon, with a posterior boundary at the rostral metencephalon, whereas Gbx2 expression in the metencephalon is bounded anteriorly by the caudal mesencephalon. The sharp boundary between the expression domains of these two genes reflects their reciprocal repression. In addition to helping form the IO molecularly, Gbx2 and Otx2 also regulate the expression of Fgf8 (fibroblast growth factor 8); Otx2 negatively regulates Fgf8 expression, whereas Gbx2 maintains its. Fgf8 is involved in regulating the various genes expressed in the mid- and hindbrain regions.

**Development of Purkinje cells** The Purkinje, Golgi, stellate and basket cells all arise from the ventricular neuroepithelium. Purkinje cells are born around E13, at which time they exit the cell cycle and migrate along the radial glial fibre system into the cerebellar anlage. Relatively little is known about the specific factors that govern Purkinje cell differentiation. Shortly after their final mitosis at E14, Purkinje cells begin to express the calcium-binding protein calbindin. Calbindin positive cells migrate from E14–E17 in a radial direction over the already formed deep cerebellar nuclei. These Purkinje cells then settle and become suspended beneath the EGL, awaiting the inward migration of granule neurons. The timely arrest of migration is dependent on the reelin pathway. Mutations in the Reelin gene or in components of its signaling pathway lead to various cerebellar defects. Although Purkinje cells depend on signals from the granule neuron precursors to migrate, their differentiation programme seems to be independent of granule neurons. Mutants that lack granule neuron precursors, such as weaver or Math1-null mice, seem to have differentiating Purkinje cells at this stage. In late embryogenesis, climbing fibres from the inferior olivary nucleus start to innervate Purkinje cells. Extensive interactions occur between the climbing fibres and the Purkinje cells, and these interactions are believed to influence Purkinje cell development. Different markers, such as NST-1 (Hsp70-4, heat-shock protein), are expressed at the time of contact. At the same time, Purkinje cells are eliminating supernumerary climbing fibre synapses in several phases, at least one of which (during postnatal days 15–16) is activity- and NMDA (N-methyl-D-aspartate)-receptor-dependent. During their final maturation phase, Purkinje cells develop extensive dendritic arbors and synapse onto granule neurons. As might be expected, this phase of development depends on granule neuron signals. In mutants such as weaver, which do not have granule neurons, dendritic trees of Purkinje cells are altered. Furthermore, culturing of Purkinje cells in vitro requires co-culturing with granule neurons for proper dendritic arborizations. Given the known role of some of the Wnt genes in axon and dendrite development, Wnt3 is a good candidate for influencing this phase of development. Wnt3 is expressed in Purkinje cells during this period, and its expression is dependent on granule neurons. Throughout the course of development, various growth factors are important for Purkinje cell growth.

**CEREBELLAR DISORDERS AND THEIR GENETIC BASIS**

1. **PROGRESSIVE MYOCLONUS EPILEPSY**: Lafora progressive myoclonus epilepsy is a brain disorder characterized by recurrent seizures (epilepsy) and a decline in intellectual function. The signs and symptoms of the disorder usually appear in late childhood or adolescence and worsen with time. Myoclonus is a term used to describe episodes of sudden, involuntary muscle jerking or twitching that can affect part of the body or the entire body. Myoclonus can occur when an affected person is at rest, and it is made worse by motion, excitement, or Bashing light (photic stimulation). In the later stages of Lafora progressive myoclonus epilepsy, myoclonus often occurs continuously and affects the entire body. Several types of seizures commonly occur in people with Lafora progressive myoclonus epilepsy. Generalized tonic-clonic seizures (also known as grand mal seizures) affect the entire body, causing muscle rigidity, convulsions, and loss of consciousness. Affected individuals may also experience occipital seizures, which can cause temporary blindness and visual hallucinations. Over time, the seizures worsen and become more difficult to treat. A life-threatening seizure condition called status epilepticus may also develop. Status epilepticus is a continuous state of seizure activity lasting longer than several minutes. About the same time seizures begin, intellectual function starts to decline. Behavioral changes, depression, confusion, and speech difficulties (dysarthria) are among the early signs and symptoms of this disorder. As the condition worsens, a continued loss of intellectual function (dementia) impairs memory, judgment, and thought. Affected people lose the ability to perform the activities of daily living by their mid-twenties, and they ultimately require comprehensive care. People with Lafora progressive myoclonus epilepsy generally survive up to 10 years after symptoms first appear.
2. **HUNTINGTON DISEASE**: Huntington disease is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition). Adult-onset Huntington disease, the most common form of this disorder, usually appears in a person's thirties or forties. Early signs and symptoms can include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions. Many people with Huntington disease develop involuntary jerking or twitching movements known as chorea. As the disease progresses, these movements become more pronounced. Affected individuals may have trouble walking, speaking, and swallowing. People with this disorder also experience changes in personality and a decline in thinking and reasoning abilities. Individuals with the adult-onset form of Huntington disease usually live about 15 to 20 years after signs and symptoms begin. A less common form of Huntington disease known as the juvenile form begins in childhood or adolescence. It also involves movement problems and mental and emotional changes. Additional signs of the juvenile form include slow movements, clumsiness, frequent falling, rigidity, slurred speech, and drooling. School performance declines as thinking and reasoning abilities become impaired. Seizures occur in 30 percent to 50 percent of children with this condition. Juvenile Huntington disease tends to progress more quickly than the adult onset form; affected individuals usually live 10 to 15 years after signs and symptoms appear.
3. **ATAXIA-TELANGIECTASIA:** This 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). The movement problems typically cause people to require wheelchair assistance by adolescence. People with this disorder also have slurred speech and trouble moving their eyes to look side-to-side (oculomotor apraxia). Small clusters of enlarged blood vessels called telangiectases, which occur in the eyes and on the surface of the skin, are also characteristic of this condition. Affected individuals tend to have high amounts of a protein called alpha fetoprotein (AFP) in their blood. The level of this protein is normally increased in the bloodstream of pregnant women, but it is unknown why individuals with ataxia telangiectasia have elevated AFP or what effects it has in these individuals. People with ataxia-telangiectasia often have a weakened immune system, and many develop chronic lung infections. They also have an increased risk of developing cancer, particularly cancer of blood-forming cells (leukemia) and cancer of immune system cells (lymphoma). Affected individuals are very sensitive to the effects of radiation exposure, including medical x-rays. The life expectancy of people with ataxia telangiectasia varies greatly, but affected individuals typically live into early adulthood

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