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DEVELOPMENTAL GENETICS OF THE CEREBELLUM

The cerebellum represents 10% of the brain's total volume, but contains about 80% of the neurons. 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, the ventricular zone(VZ), from which most cells are derived and the rhombic lip, the specialized germinal matrix from which granule neurons are derived.

Development of the cerebellum occurs in four basic stages:

• In the first stage, characterization of cerebellar territory occurs at the midbrain–hindbrain boundary. Transplantation studies in chicken and mouse have found that the isthmus organizer (IsO), a region corresponding to the midbrain–hindbrain boundary expression, is crucial for specifying midbrain and cerebellar structures. At the isthmus, restricted expression of secreted factors, such as fibroblast growth factor 8, FGF8 and Wnt1, the mammalian homolog of Drosophila wingless gene, as well as homeobox proteins En1 and En2 and paired box genes Pax2 and Pax5 are required for early specification of midbrain and hindbrain structures.

• In the second stage, two compartments for cell proliferation are formed. Purkinje cells and cells of the deep cerebellar nuclei are generated in the roof of the fourth ventricle and granule cell precursors, as well as cells of the precerebellar nuclei are formed in the rhombic lip. Development of Purkinje cells is not well understood, but they are known to secrete Sonic hedgehog which regulates proliferation of granule cells. By this time point, granule neuron precursors express a number of markers, Math1, nestin, zipro1/RU49 and Zic genes 1, 2. Purkinje cells migrate radially to their final positions, whereas granule neurons migrate over the surface of the developing cerebellum, forming the external granule layer (EGL).

• In the third stage, cells of the EGL(External Granular Layer) migrate inward along the processes of Bergman glia to their final position in the internal granular layer (IGL).

• Finally, cerebellar circuitry is established and further differentiation occurs. The lower portion of the rhombic lip also gives rise to cells of the precerebellar nuclei such as the inferior olivary nuclei, which migrate to positions in the brainstem.

GENETIC BASES OF KNOWN CEREBELLAR DISORDERS

● DANDY-WALKER MALFORMATION (DWM)

It is a rare congenital brain malformation in which the part joining the two hemispheres of the cerebellum (the cerebellar vermis) does not fully form, and the fourth ventricle and space behind the cerebellum (the posterior fossa) are enlarged with cerebrospinal fluid.

Dandy-Walker malformation has also been associated with many chromosomal abnormalities. This condition can be a feature of some conditions in which there is an extra copy of one chromosome in each cell (trisomy). Dandy-Walker malformation most often occurs in people with trisomy 18.

Dandy-Walker malformation can also be a feature of genetic syndromes that are caused by mutations in specific genes.

● CEREBELLAR HYPOPLASIA

Cerebellar hypoplasia is a neurological condition in which the cerebellum is smaller than usual or not completely developed. It is believed that the cerebellar hypoplasia is due to a defect in the neuronal proliferation and neuronal migration during development of the embryonic nervous system. It may result after an atrophy (destruction) of the cerebral cortex on the opposite side.

The oligophrenin 1 gene (OPHN1) is a protein with a Rho-GTPase-activating domain required in the regulation of the G-protein cycle. Mutations in the OPHN1 cause X-linked mental retardation (XLMR) with cerebellar hypoplasia and distinctive facial appearance.

● JOUBERT SYNDROME

Joubert syndrome (JS) is an autosomal recessive neurodevelopmental disorder, which is characterized by the molar tooth malformation (MTM), a complex brainstem malformation that reflects aplasia or marked hypoplasia of the cerebellar vermis, thickened and elongated superior cerebellar peduncles and a deepened interpeduncular fossa at the midbrain–hindbrain junction.

Ten genes have been identified that cause Joubert syndrome. A mutation in the AHI1 (JBTS3) gene is responsible for this condition in approximately 11% of families. Affected individuals with this gene mutation often have impaired vision due to retinal dystrophy. A mutation in the NPHP1 (JBTS4) gene causes approximately 1-2% of Joubert syndrome. Affected individuals with this gene mutation often develop a progressive kidney disease called nephronophthisis. A mutation in the CEP290 (JBTS5) gene causes about 4-10% of Joubert syndrome. Mutations in the TMEM67 (JBTS6), JBTS1, JBTS2, JBTS7, JBTS8 and JBTS9 genes are also associated with Joubert syndrome. Other genes responsible for this condition are currently unknown.