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CEREBELLUM AND ITS CONNECTIONS

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

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 that is apparent on axial MRI at the midbrain–hindbrain junction. Clinically, classic JS is associated with neonatal hypotonia (loss of muscle tone), ataxia, developmental delay, mental retardation, and often neonatal apnea/hyperpnea (irregular breathing) and/or ocular motor apraxia (difficulties in initiating rapid horizontal eye movements—saccades). Autistic features have also been reported as a relatively common component of JS .

None of these features alone is diagnostic of JS, however, and in more recent years, it has become obvious that JS is a part of a spectrum of disorders involving vermis hypoplasia and the MTM. Some of these include COACH (OMIM 216360), referring to characteristic hallmarks of cerebellar vermis hypoplasia, oligophrenia (mental impairment), congenital ataxia, ocular coloboma and hepatic fibrosis; and Váradi Papp or orofaciodigital VI syndrome (OMIM 277170), defined by midline facial or hand abnormalities.

Varying degrees of extra-CNS involvement have further complicated diagnosis, including ocular colobomas, postaxial polydactyly, liver fibrosis, cystic dysplastic kidneys, retinopathy and/or nephronophthisis (NPHP). These features significantly overlap with other disorders with cerebello-oculo-renal involvement, most notably NPHP; the significance of this relationship is strengthened by the identification of deletions of NPHP1, a gene commonly mutated in NPHP in a subset of JS patients .