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Write a concise review on the development genetics of the cerebellum and highlight genetic basis of a known cerebellar disorder

The cerebellum is one of the first brain structures to begin to differentiate, yet it is one of the last to achieve maturity — the cellular organization of the cerebellum continues to change for many months after birth. This protracted developmental process creates a special susceptibility to disruptions during embryogenesis and makes the cerebellum highly amenable to study. Over the past few years, genetic research has provided a great deal of information about the molecular events directing the formation of the cerebellum. Knowledge of these mechanisms should enable us to address the nature of human diseases that have their root in developmental processes. The internal structure of the cerebellum reflects an intriguing paradox; its cytoarchitecture is relatively simple and repeated throughout, yet the connections between its neurons are wired into a complex array of gene expression domains and functional circuits. The developmental mechanisms that coordinate the establishment of cerebellar structure and circuitry provide a powerful model for understanding how functional brain networks are formed. Two primary germinal zones generate the cells that make up the cerebellum. Each zone expresses a specific set of genes that establish the cell lineages within the cerebellar anlage. Then, cohorts of differentiated projection neurons and interneuron progenitors migrate into the developing cerebellum. Thereafter, a number of remarkable patterning events occur including transformation of the smooth cerebellar surface into an intricately patterned series of folds, formation of three distinct cellular layers, and the demarcation of parasagittal gene expression domains. Together, these structural and molecular organizations are thought to support the proper connectivity between incoming afferent projections and their target cells. After birth, genetic programs and neural activity repattern synaptic connections into topographic neural networks called modules, which are organized around a longitudinal zone plan and are defined by their molecular, anatomic, and functional. 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.

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.Because the pathology of JS suggests defects of early cerebellar development, particularly of structures derived from the primitive isthmus (45), genes involved in cerebellar patterning at the IsO have been tested as candidate genes, especially those with comparable phenotypes in mouse models. The *swaying* mouse, which was shown to have a truncation mutation of *Wnt1*, has a phenotype reminiscent of JS, i.e. ataxia, and agenesis of cerebellar structures (46). Mutant alleles of *Fgf8, En1*and *En2* also result in cerebellar abnormalities. A hypomorphic allele of *Fgf8* was shown to cause deletion of midbrain and hindbrain structures (47). *En1* and *En2* mice also manifest absent or abnormal cerebellar structures (48,49). Mutations in these genes, however, could not be identified in JS patients screened thus far, suggesting that they are not likely to be a common cause of JS (50,51).

The *ZIC* (zinc fingers in the cerebellum) family of transcription factors were named for their exclusively cerebellar expression in adults. Embryonically, they are more widely distributed and have been implicated in a variety of developmental functions (52,53). *Zic1* mutant mice have hypoplastic cerebella that are missing anterior lobules of the vermis (54). They also have behavioral deficits of ataxia and hypotonia, as in patients with JS, and were thought to be a good model for the disease (55). However, in an analysis of 35 JS pedigrees, *ZIC1* was also excluded as a causative gene (56). In fact, heterozygous mutations in *ZIC1* and *ZIC4* have been reported to be a cause of the related, but distinct Dandy–Walker malformation, characterized by hypoplasia and upward rotation of the vermis, cystic enlargement of the fourth ventricle and often hydrocephalus.

Wang V.Y,Zoghibi H.Y.2001. Genetic regulation of cerebral development.Nature reviews neuroscience.2:484-491

# Louie C.M and Gleason J.G.2005.Genetic basis of Joubert syndrome and related disorders of cerebellar development.Human molecular genetics.14:235-242

White J.J and Sillitoe V.R.2012.Development of the cerebellum: from gene expression patterns to circuit maps.Developmental biology.2