**ASSIGNMENT**

**QUESTION:** WRITE A CONCISE REVIEW ON THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM AND HIGHLIGHT THE GENETIC BASES OF KNOWN CEREBELLAR DISORDERS.

**ANSWER**

ABSTRACT

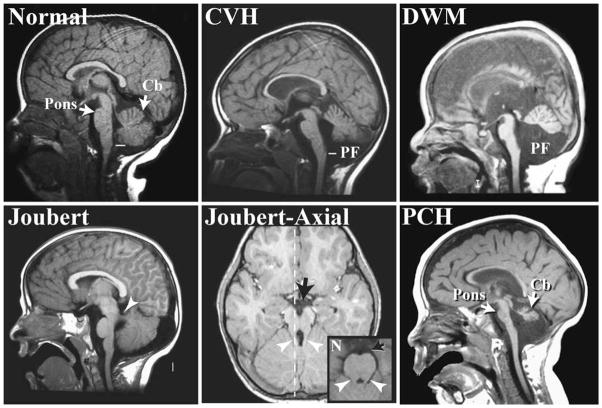
The internal structure of the cerebellum reflects an intriguing paradox; its cytoarchitecture is relatively simple and repeated throughout, yet the connections between its neurons are wired into a complex array of gene expression domains and functional circuits. The developmental mechanisms that coordinate 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 properties.

The mature cerebellum has exquisite, stereotypical morphology, foliation, and lamination, which are consistent between individuals and highly conserved across vertebrates. At the cellular level, unlike other regions of the CNS, the cerebellum is composed of very few neuronal types, each with distinct morphology, arranged in discrete lamina, and connected in stereotypical circuits [[9](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R9)]. The cerebellum has essential roles in motor coordination, but is not essential for viability. Thus, compared with other regions of the central nervous system (CNS) the cerebellum has been more amenable to genetic studies since disruptions in development, which lead to abnormal morphology or function, are readily observed in obvious neurological and behavioural phenotypes. Because of this, it has been possible to obtain a precise understanding of cerebellar development [[10](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R10)–[14](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R14)]

The study of human cerebellar malformations is beginning to provide new insights regarding the basic developmental principles of the cerebellum. Currently, human patient populations with congenital developmental disorders are largely underutilized in basic research but they have proven to be valuable for identifying novel, significant developmental genes. As in the mouse, disruption of human cerebellar development is often severely handicapping but not lethal, making it amenable to genetic analysis. Also similar to mice, the structure of the human cerebellum facilitates the easy identification of malformations as its morphology, foliation, and lamination are stereotypical across individuals and its morphogenesis is well understood. In conjunction with advances in imaging techniques, this allows patients to be diagnosed with malformations at early post-natal or even fetal stages. While patient populations provide a great resource for researchers, they are not often employed due to several difficulties, including a lack of routine brain imaging on patients with developmental abnormalities, genetic heterogeneity among cerebellar patients resulting in the requirement of large sample sizes, and difficulties recruiting patients. Despite these obstacles, human cerebellar malformations have been used to identify cerebellar developmental genes [[11](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R11), [54](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R54)]. Gratifyingly, mutations in human RELN cause cerebellar hypoplasia, similar to the phenotype seen in the reeler mouse [[55](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R55)], demonstrating the validity of cross species comparisons. Once genes have been identified in human cerebellar malformation syndromes, mouse models have proven essential for deciphering the underlying developmental disruptions [[11](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R11)].

**TYPES OF HUMAN CEREBELLAR MALFORMATIONS**

Advances in imaging, genetics, and classification are enabling previously consolidated malformations to be delineated into distinct categories [[56](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R56), [57](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R57)]. Here we will discuss cerebellar vermis hypoplasia (CVH), DWM, Joubert syndrome and related disorders (JSRD), and pontocerebellar hypoplasia (PCH). The defining features of these diagnoses are based on imaging criteria rather than clinical outcome, with most of these diagnoses associated with intellectual and motor disabilities. CVH is characterized by a small hypoplastic cerebellum with the vermis more affected than the hemispheres. DWM includes CVH; however, there is also an upward rotation of the cerebellar vermis that results in an enlarged fourth ventricle, and an increased size of the posterior fossa. DWM is the most common cerebellar malformation, with an estimated incidence of approximately 1 in 5,000. CVH is also relatively common and often confused with DWM, making estimations of incidence problematic. CVH and DWM often present as sporadic cases, although there are several CVH loci with known recessive or X-linked inheritance. Mendelian inheritance for DWM is rare, and the genetics are likely oligogenic. In contrast, JSRD are most often autosomal recessive disorders and are rare, with a population incidence estimated to be 1/100,000. As a group, JSRD are characterized by cerebellar vermis hypoplasia plus the presence of elongated cerebellar peduncles and a deepened interpeduncular fissure that appear as a “molar tooth” on axial brain scans. In addition, these patients exhibit axon guidance defects that include a decussation failure of the pyramidal tract and superior cerebellar peduncles. Patients with PCH exhibit a heterogeneous set of malformations characterized by hypoplasia and atrophy of the cerebellum, inferior olive, and ventral pons. This degenerative disorder often begins with embryonic atrophy of these regions.

[[](https://www.ncbi.nlm.nih.gov/core/lw/2.0/html/tileshop_pmc/tileshop_pmc_inline.html?title=Click%20on%20image%20to%20zoom&p=PMC3&id=2921561_nihms199070f1.jpg)](https://www.ncbi.nlm.nih.gov/core/lw/2.0/html/tileshop_pmc/tileshop_pmc_inline.html?title=Click%20on%20image%20to%20zoom&p=PMC3&id=2921561_nihms199070f1.jpg" \t "tileshopwindow)

[Fig. 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/figure/F1/)

Magnetic resonance images (*MRI*) showing sagittal views of the cerebellar vermis from a subset of human cerebellar malformations. The image of a patient with cerebellar vermis hypoplasia (*CVH*) shows decreased vermis size that does not reach the obex, the narrowing of the fourth ventricle in the caudal medulla (*white line*), as occurs in normal subjects. In addition to vermis hypoplasia, subjects with Dandy–Walker malformation (*DWM*) also exhibit an increased posterior fossa size and an upward rotation of the vermis. The parasagittal image of a patient with Joubert syndrome shows vermis hypoplasia and an elongated superior cerebellar peduncle (*white arrowhead*). The plane of this off-midline image is designated with a *dotted white line* in the corresponding axial image. The “molar tooth” malformation of Joubert syndrome and related disorders can be seen in the axial MRI as elongated cerebellar peduncles (*white arrowhead*) and deepened interpeduncular fossa (*black arrow*) compared with a normal subject (N; inset). Subjects with pontocerebellar hypoplasia (*PCH*) exhibit both decreased vermis size and pontine hypoplasia (*arrows*). *Cb* cerebellum, *PF* posterior fossa

**Causative Genes in Human Cerebellar Malformations**

In the last decade, there has been considerable effort in defining the genetic basis of human cerebellar malformations. Causative genes include those involved in cerebellar patterning, cell fate specification, and other developmental processes.

List of genes and suspected cellular processes that have been implicated in human cerebellar malformations (see text for discussion)

| **Cerebellar malformations** | **Implicated human genes** | **Likely disrupted process** |
| --- | --- | --- |
| Cerebellar vermis hypoplasia (CVH) | *OPHN1* [[59](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R59), [60](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R60)] | Spine morphogenesis |
| Dandy–Walker malformation (DWM) | *ZIC1*, *ZIC4* [[65](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R65)], *FOXC1* [[17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R17)] | Granule cell differentiation |
| Joubert syndrome and related disorders (JSRD) | *AHI1* [[67](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R67), [68](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R68)], *ARL13B* [[69](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R69)], *CCD2A* [[70](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R70), [71](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R71)], *CEP290* [[72](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R72), [73](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R73)], *INPP5E* [[74](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R74), [75](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R75)], *NPHP1* [[76](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R76), [77](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R77)], *RPGRIP1L* [[78](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R78), [79](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R79)], and *TMEM67* [[80](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R80)] | Granule cell proliferation |
| Pontocerebellar hypoplasia (PCH) | *CASK* [[86](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R86)], *RARS2* [[88](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R88)], *TSEN54*, *TSEN34*, and *TSEN2* [[89](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/#R89)] | Spine development, cell proliferation, tRNA splicing, cellular maintenance. |

**CONCLUSION**

Our current understanding of the molecular and genetic basis of cerebellar development is derived primarily from the study of spontaneous and targeted mouse mutants. Only recently have human patients with cerebellar malformations begun to contribute to the discovery of genes that regulate the development of the cerebellum. Continued advances in the genomic technologies described here will facilitate the identification of other causative genes in human cerebellar malformations. In conjunction with continued use of model vertebrates, these novel approaches will yield additional genes—and hence networks—required in normal cerebellar development.

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