**NAME: DARA SANCTUS MATRIC NUMBER: 17/MHS01/096 COURSE: ANA 303 DEPARTMENT:MBBS**

**Question:** Write a concise review on the developmental genetics of the cerebellum and highlight the genetic basis of known cerebellar disorders.

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.

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 in

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.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.

**Some known cerebellar disorders include:**

Here we will discuss cerebellar vermis hypoplasia (CVH), DWM, Joubert syndrome and related disorders (JSRD), and pontocerebellar hypoplasia (PCH) ([Fig. 1](/pmc/articles/PMC2921561/figure/F1/?report=objectonly)). 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 [[57](" \l "R57), [58](" \l "R58)]. 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 [[59](" \l "R59)–[61](" \l "R61)]. Mendelian inheritance for DWM is rare, and the genetics are likely oligogenic [[58](" \l "R58), [62](" \l "R62)]. In contrast, JSRD are most often autosomal recessive disorders and are rare, with a population incidence estimated to be 1/100,000 [[57](" \l "R57)]. 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.

Pancreas specific transcription factor 1a (Ptf1a) was initially implicated as a basic helix–loop–helix transcription factor in pancreatic development since mice with a targeted deletion lacked pancreatic tissue [[63](" \l "R63)]. However, its role in brain development was not investigated until truncations of this gene were found to result in cerebellar agenesis in multiple families [[54](" \l "R54)]. Further investigations determined that loss of Ptf1a causes a failure to generate GABAergic cerebellar neurons in the embryonic cerebellar anlage in both human and mouse [[64](" \l "R64)]. Since Purkinje cells, which are GABAergic, are also required for the proliferation of cerebellar granule neurons, humans and mice lacking Ptf1a exhibit profound cerebellar agenesis [[64](" \l "R64)].

Transcription factors have also been implicated in other types of cerebellar malformations. Heterozygous loss of the ZIC1 and ZIC4 genes encoding zinc finger transcription factors can cause DWM, a phenotype which is mimicked in Zic1 and Zic4 double heterozygous mutant mice [[65](" \l "R65)]. Mutations in FOXC1, a transcription factor gene located in the 6p25.3 locus, have recently been shown to contribute to human DWM [[17](" \l "R17)]. Mouse models have demonstrated that Foxc1 is developmentally expressed in the mesenchyme adjacent to the cerebellum, where it is critical for normal posterior fossa development [[66](" \l "R66)]. In addition to regulating skull development, Foxc1 controls mesenchymally expressed signaling molecules including Bmp2 and Bmp4 [[17](" \l "R17)]. Loss of these signaling molecules causes the adjacent cerebellar rhombic lip to lose Atoh1 (Math1) expression, a gene critical for normal granule cell differentiation. These findings, based on studies in both human and mice, have surprisingly implicated mesenchymal signaling as a critical regulator of early cerebellar anlage development.

Studies of JSRD patients have also provided surprising insights into new developmental mechanisms. Of the nine loci linked to JSRD, eight have been cloned and the following causative genes identified: AHI1 [[67](" \l "R67), [68](" \l "R68)], ARL13B [[69](" \l "R69)], CC2D2A [[70](" \l "R70), [71](" \l "R71)], CEP290 [[72](" \l "R72), [73](" \l "R73)], INPP5E [[74](" \l "R74), [75](" \l "R75)], NPHP1 [[76](" \l "R76), [77](" \l "R77)], RPGRIP1L [[78](" \l "R78), [79](" \l "R79)], and TMEM67 [[80](" \l "R80)]. Many of these genes are implicated in normal ciliary function and their protein products localize to the cilia or basal bodies. One such cilia-related protein is Nephrocystin, the product of NPHP1, which interacts with beta-tubulin and localizes to primary cilia [[81](" \l "R81)]. In cell culture, CEP290, centrosomal protein 290, is involved in ciliogenesis, localizes to centrioles in a microtubule-dependent manner, and regulates the microtubule network, as shown through RNAi. Furthermore, CEP290 interacts with the protein product of CCD2A both genetically and physically [[71](" \l "R71)]. Most recently, mutations in the INPP5E gene, which codes for inositol polyphosphate-5-phosphatase E, were found in patients with Joubert syndrome. While it was known that this enzyme hydrolyzes phosphatidylinositols, INPP5E was found to be localized to cilia and mutations resulted in premature destabilization of cilia after stimulation [[74](" \l "R74), [75](" \l "R75)]. Thus, examination of human patients led to a novel role for INPP5E in both cilia signaling and Joubert syndrome. Mutations in many components of this single biological pathway result in similar cerebellar defects. The actual purpose of cilia in the cerebellum is likely to be linked to SHH signaling. Significantly, loss-of-function mutations in murine Kif3a and Ift88—genes encoding intraflagellar transport proteins for the formation and maintenance of cilia—cause SHH-dependent proliferation defects of granule cell progenitors. This loss of SHH signaling results in cerebellar phenotypes resembling those seen in JSRD [[82](" \l "R82), [83](" \l "R83)]. JSRD now provide a model for how studies of human cerebellar malformations can lead to the discovery of causative genes and expand our knowledge of the pathways involved in cerebellar development.

Additional molecules have been implicated in human cerebellar malformations, which are certain to illuminate new cerebellar developmental mechanisms. Deletions of the Rho-GAP protein encoding gene Oliogphrenin-1(OPHN1) have been found in multiple families with X-linked CVH [[59](" \l "R59), [60](" \l "R60)]. While Ophn1 is required for the stabilization of glutamatergic spines [[84](" \l "R84)], it has not been implicated in regulating earlier developmental events such as cell division. Interestingly, mice with a targeted deletion of Ophn1 exhibit learning deficits and have dilated lateral and third ventricles, but their cerebellar size and morphology are normal [[84](" \l "R84)]. This suggests that the mental retardation (MR) seen in human patients may not be due to cerebellar defects. However, until the connectivity and plasticity of the mutant mouse cerebellum are examined in detail this only remains a speculation. Recently Ophn1 has been shown to facilitate clathrin-mediated endocytosis of post-synaptic vesicles, including the AMPA receptor, by repressing the RhoA/ROCK pathway [[85](" \l "R85)]. Because of this, mutant mice lack LTD in the hippocampus. Cerebellar LTD still remains to be examined.

Mutations of another molecule with a known role in synapse development have also been seen in PCH [[86](" \l "R86)]. CASK is a calcium/calmodulin-dependant serine/threonine kinase localized to synapses via membrane-associated molecules, including Neurexin. CASK also regulates gene transcription during cell proliferation [[87](" \l "R87)]. Although mouse Cask mutants have cerebellar hypoplasia, the developmental basis for this pathology has not yet been studied [[86](" \l "R86)]. Genes from the tRNA splicing pathway have also been observed to cause PCH when mutated in humans. One family has been found with three members containing mutations in the RARS2 gene, which encodes mitochondrial arginine-transfer RNA synthase [[88](" \l "R88)]. Individuals with PCH have also been found to have mutations in TSEN54, TSEN34, and TSEN2, which all encode tRNA splicing proteins [[89](" \l "R89)]. The study of mouse models will be essential to determine why developing cerebellar and pontine cells are particularly sensitive to the loss of these genes even though they are ubiquitously expressed.

Human studies have demonstrated that patient clinical phenotypes associated with severe congenital cerebellar malformations described here can be highly variable. Less severe cerebellar malformations have been reported in patients with non-syndromic MR [[57](" \l "R57)], Autism Spectrum Disorders, and schizophrenia [[90](" \l "R90)–[93](" \l "R93)]. Evidence of Purkinje cell dysfunction in cerebella from autistic patients has been demonstrated by reduced levels of glutamate decarboxylase(GAD67), which codes for a GABA-synthesizing enzyme [[94](" \l "R94)]. In addition, levels of various gene transcripts involved in GABAergic transmission are altered in lateral cerebellar hemispheres of schizophrenic patients. Specifically, GAD67, GAD65, GAT-1, MGLUR2, and NOS1 were downregulated whereas GABAA-alpha6, GABAA-delta, GLUR6, and GRIK5 were upregulated [[95](" \l "R95)]. Thus, it is likely that the genes underlying these more common and genetically complex neurodevelopmental disorders also influence cerebellar development. Notably, most patients with MR, autism, and other neurodevelopmental disorders rarely undergo brain imaging. Therefore, the coincidence of these disorders with cerebellar malformation is often missed. In order to fully and accurately delineate clinical phenotypes, we strongly advocate routine brain imaging of all human neurodevelopmental disorders. Further, given the extremely fine resolution with which cerebellar phenotypes can now be characterized in mice at the molecular, cellular, and systems level, mouse models for these common neurodevelopmental disorders are certain to be highly informative regarding their underlying pathology.

**REFERENCES**  <https://scholar.google.com/scholar?hl=en&as_sdt=0,5&qsp=1&q=genetic+basis+cerebellar+development&qst=br>

Wassarman, K. M. et al. Specification of the anterior hindbrain and establishment of a normal mid/hindbrain organizer is dependent on *Gbx2* gene function. *Development* **124**, [2923–2934](tel:2923–2934) (1997).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/

Hallonet, M. E., Teillet, M. A. & Le Douarin, N. M. A new approach to the development of the cerebellum provided by the quail–chick marker system. *Development* **108**, 19–31 (1990).**Describes the lineage analysis experiments that revealed the dual origin of the cerebellum from the mesencephalon and metencephalon.**