**OKE SUCCESS OLUWASEYI**

**17/MHS01/243**

**MEDICINE AND SURGERY**

The Cerebellum is best known for its role in integrating sensory information from the periphery to guide movement and balance. Reflecting its participation in diverse neurocognitive tasks, abnormal cerebellar development is associated with intellectual disability, autism spectrum disorder, and attention-deficit/hyperactivity disorder. The mature cerebellum has three superficial layers, consisting of **outer molecular**, **intermediate Purkinje cell**, and **inner granular layers** that are separated from the deep cellular nuclei by interposed white matter. Human cerebellar development extends from 30 days Postconception to the second PostNatal year, whereas the human brainstem cranial nerve nuclei and the latest developing neocortical region, the frontal cortex are established by the first and third trimesters, respectively. Its protracted development makes the human cerebellum vulnerable to environmental perturbations resulting in structural abnormalities and tumors. The major cell types of the cerebellum consist of **glutamatergic**, **GABAergic**, and **glial** **cells**. Mediolateral compartmentalization of the cerebellum is determined on the ‘birth date” of the Purkinje cells.

 Glutamatergic, excretory cell types consist of granule, unipolar brush cell, and deep cerebellar nuclear neurons, where Purkinje cells, interneurons, and a contigent of deep cerebellar nuclear neurons are GABAergic, inhibitory cells. At 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. In comparism to 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. The mechanism decoded from the study of cerebellar development have broad applicability to other CNS regions such as **CEREBRAL** **CORTEX**. For example, while initial insights regarding the function of ***Reelin*** ***gene*** were gleaned from studying the cerebella of reeler mice, recent studies have revealed that this gene is required for emigration of **denate** **gyrus** progenitors from a transient **subpial** **zone** and into the **subgranular** **zone**. Also while *Foxc1* controls normal cerebellar and posterior fossa development by regulting secreted growth factor signals from the mesenchyme, it is also required for the development of meningeal structures that in turn influence skull and cortical development.

Advances in imaging, genetics, and classification are enabling previously malformations can be delineated into distinct categories.

**CEREBELLAR VERMIS HYPOPLASIA(CVH):** it is characterized by a small hypoplastic cerebellum with the vermis more affected than the hemispheres. CVH is also relatively common and often confused with DWM. It is present as sporadic cases, although here are several CVH loci with known recessive or X-linked inheritance. Mendelian inheritance for DWM is rare, and the genetics are likely oligogenic.

**DWM (DANDY-WALKER MALFORMATION):** This 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. They are often present as sporadic cases. ***ZIC1***and ***ZIC4*** genes encoding zinc finger transcription factor can cause DMW. Mutations in ***FOXC1***, a transcription factor gene located in the locus, have recently been shown to contribute to human DWM.

**JSRD (JOUBERT SYNDROME):** They are most often autosomal recessive disorders and are rare, with a population incidence estimated to be 1/100000. 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.

**PCH (PONTOCEREBELLAR HYPOPLASIA):** Mutations of another molecule with a known role in synapse development have also been seen in PCH. Genes from the tRNA splicing pathway have also been studied to cause PCH when mutated in humans. A family has been found with three members containing mutations in the ***RARS2*** gene, which encodes mitochondrial arginine-transfer RNA synthase. Individuals with PCH have also been found to have mutations in **TSEN54**, **TSEN34**, **TSEN2**, which all encode tRNA splicing proteins.

 Human studies have demonstrated that patient clinical phenotypes associated with severe congenital cerebellar. Less severe cerebellar malformations have been reported in patients with non-syndromic **MR,** Autism Spectrum Disorders and Schizophrenia. Evidence of Purkinje cell dysfunction in cerebella from autistic patients has been demonstrated by reduced level of ***Glutamate*** ***Decarboxylase*** (***GAD67***), which codes for a GABA-synthesizing enzyme. 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, there should be routine brain imaging of all human neurodevelopmental disorders.

**REFERENCES**

1.Herrup K, Mullen RJ. Staggerer chimeras: intrinsic nature of Purkinje cell defects and implications for normal cerebellar development. Brain Res. 1979;178(2–3):443–57. [PubMed] [Google Scholar]

Chizhikov V, Millen KJ. Development and malformations of the cerebellum in mice. Mol Genet Metab. 2003;80(1–2):54–65. [PubMed] [Google Scholar]

2. Millen KJ, Gleeson JG. Cerebellar development and disease. Curr Opin Neurobiol. 2008;18(1):12–9. [PMC free article] [PubMed] [Google Scholar]

3. Carletti B, Rossi F. Neurogenesis in the cerebellum. Neuroscientist. 2008;14(1):91–100. [PubMed] [Google Scholar]

4. Alkan O, Kizilkilic O, Yildirim T. Malformations of the midbrain and hindbrain: a retrospective study and review of the literature. Cerebellum. 2009;8(3):355–65. [PubMed] [Google Scholar]

5. Manto M. The cerebellum, cerebellar disorders, and cerebellar research—two centuries of discoveries. Cerebellum. 2008;7 (4):505–16. [PubMed] [Google Scholar]

Aldinger KA, Lehmann OJ, Hudgins L, Chizhikov VV, Bassuk AG, Ades LC, et al. FOXC1 is required for normal cerebellar development and is a major contributor to chromosome 6p25.3 Dandy–Walker malformation. Nat Genet. 2009;41 (9):1037–42. [PMC free article] [PubMed] [Google Scholar]

Google Scholar]

6. Hong SE, Shugart YY, Huang DT, Shahwan SA, Grant PE, Hourihane JO, et al. Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with human RELN mutations. Nat Genet. 2000;26(1):93–6. [PubMed] [Google Scholar]

7. Barkovich AJ, Millen KJ, Dobyns WB. A developmental and genetic classification for midbrain-hindbrain malformations. Brain. 2009 in press. [PMC free article] [PubMed] [Google Scholar]

8. Millen KJ, Grinberg I, Blank M, Dobyns WB. ZIC1, ZIC4 and Dandy–Walker malformation. In: Epstein CJ, Erickson RP, Wynshaw-Boris A, editors. Inborn errors of development. 2. Oxford University Press; Oxford: 2008. [Google Scholar]

9. Bergmann C, Zerres K, Senderek J, Rudnik-Schoneborn S, Eggermann T, Hausler M, et al. Oligophrenin 1 (OPHN1) gene mutation causes syndromic X-linked mental retardation with epilepsy, rostral ventricular enlargement and cerebellar hypoplasia. Brain. 2003;126(Pt 7):1537–44. [PubMed] [Google Scholar]

10. Grinberg I, Northrup H, Ardinger H, Prasad C, Dobyns WB, Millen KJ. Heterozygous deletion of the linked genes ZIC1 and ZIC4 is involved in Dandy–Walker malformation. Nat Genet. 2004;36(10):1053–5. [PubMed] [Google Scholar]

11. Sathyanesan A, Zhou J, Scafidi J, Heck DH, Sillitoe RV, Gallo V. Emerging connections between cerebellar development, behaviour and complex brain disorders. Nat Rev Neurosci. 2019;20(5):298–313. doi: 10.1038/s41583-019-0152-2 pmid:30923348.

12. Rakic P, Sidman RL. Histogenesis of cortical layers in human cerebellum, particularly the lamina dissecans. J Comp Neurol. 1970;139(4):473–500. doi: 10.1002/cne.901390407 pmid:4195699.

13. Yachnis AT, Rorke LB. Cerebellar and brainstem development: an overview in relation to Joubert syndrome. J Child Neurol. 1999;14(9):570–3. doi: 10.1177/088307389901400904 pmid:10488901.

14. Pascual M, Abasolo I, Mingorance-Le Meur A, Martinez A, Del Rio JA, Wright CV, et al. Cerebellar GABAergic progenitors adopt an external granule cell-like phenotype in the absence of Ptf1a transcription factor expression. Proc Natl Acad Sci U S A. 2007;104(12):5193–8. doi: 10.1073/pnas.0605699104 pmid:17360405; PubMed Central PMCID: PMC1829285.