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**Question:**

Write a concise review on the developmental genetics of the cerebellum and highlight the genetic bases of known cerebellar disorders.

**Developmental Genetics of the Cerebellum**

 The list of genes that when mutated cause disruptions in cerebellar development is rapidly increasing. The study of both spontaneous and engineered mouse mutants has been essential to this progress, as it has revealed much of our current understanding of the developmental processes required to construct the mature cerebellum. Improvements in brain imaging, such as magnetic resonance imaging (MRI) and the emergence of better classification schemes for human cerebellar malformations, have recently led to the identification of a number of genes which cause human cerebellar disorders. Advances in brain imaging techniques and improvements in the classification of human cerebellar malformations have further aided the discovery of genes regulating cerebellar development.

 The cerebellum is best known for its role in integrating sensory information from the periphery to guide movement and balance. Increasingly, roles in motor learning, multimodal sensory integration, cognition, emotion, and social behavior are also recognized that are all sub served by a restricted set of neurons with stereotyped connectivity. 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 cell layers, consisting of outer molecular, intermediate Purkinje cell, and inner granular layers that are separated from the deep cerebellar 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. Moreover, in the mouse, the cerebellum develops over 30–35 days. 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. Glutamatergic, excitatory cell types consist of granule, unipolar brush cell, and deep cerebellar nuclear neurons, whereas Purkinje cells, interneurons, and a contingent of deep cerebellar nuclear neurons are GABAergic, inhibitory cells. Each cell type displays complex migratory patterns to occupy defined positions in the mature cerebellum that are linked to its birth order from the germinal zones of the cerebellar anlage. The current understanding of cerebellar development has largely been derived from gene expression, lineage tracing, and genetic perturbation studies in the mouse, whose cell types, lamination, circuitry, and basic foliation patterns closely resemble those in humans.

 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.

**Genetic Bases of Known Cerebellar Disorders**

 In addition to spontaneous and targeted mouse mutants, 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. Gratifyingly, mutations in human RELN cause cerebellar hypoplasia, similar to the phenotype seen in the Reeler mouse, 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.

 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:

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| **Cerebellar Malformations** | **Implicated Human Genes** | **Likely Disrupted Process** |
| Cerebellar vermis hypoplasia (CVH) | *OPHN1* | Spine morphogenesis |
| Dandy-Walker malformation (DWM) | *ZIC1, ZIC4, FOXC1* | Granule cell differentiation |
| Joubert syndrome and related disorders (JSRD) | *AHI1, ARL13B, CCD2A, CEP290, INPP5E, NPHP1, RPGRIP1L* and *TMEM67* | Granule cell proliferation |

Normal cerebellar growth and morphogenesis depends on the integrity of the primary cilium that functions as a cellular ‘antenna’. Although most cells possess primary cilia, other cell types possess specialized motile or nonmotile cilia. The primary cilium acts as a signaling hub, best known for its role in transducing signaling by the diffusible morphogen sonic hedgehog (SHH).

 In humans, a 2.3-Mb deletion of chromosome 8p21.2–21.3 proximal to FGF17 leads to a marked reduction in FGF17 expression and is associated with vermis hypoplasia (Dandy–Walker malformation). In the X-linked Opitz syndrome, characterized by cerebellar midline defects, including vermis hypoplasia, the mutated gene, midline 1 (MID1), which encodes a ubiquitin ligase, lies genetically upstream of FGF17. Therefore, distinct genetic programmes confined to specific cell types and locations regulate cerebellar vermis and hemisphere development.

**References:**

* Joshua J. White, Roy V. Sillitoe. Development of the Cerebellum: From Gene Expression Patterns to Circuit Maps. PMID: 23799634
* Samin A. Sajan, Kathryn E. Waimey, Kathleen J. Millen. Novel Approches to Studying the Genetic Basis of Cerebellar Development. 2010; 27 ̶ 283. PMID: 20387026
* Max J. van Essen, Samuel Nayler, Esther B. E. Becker, John Jacob. Deconstructing Cerebellar Development Cell by Cell. 2020