**ASSIGNMENT ON NEUROANATOMY**

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**ASSIGNMENT TITLE:** CEREBELLUM AND ITS CONNECTIONS (ANA 303)

**LEVEL:** 300

**QUESTION:**

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

Answer

**ABSTRACT:**

The list of genes that when mutated cause disruptions in cerebellar development is rapidly increasing. 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.

**DISCUSSION:**

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. 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 behavioral phenotypes. Because of this, it has been possible to obtain a precise understanding of cerebellar development. The mechanisms deciphered from the study of cerebellar development have broad applicability to other CNS regions such as the cerebral cortex. For example, while initial insights regarding the function of the Reelin gene were gleaned from studying the cerebella of reeler mice, recent studies have revealed that this gene is required for the emigration of dentate gyrus progenitors from a transient subpial zone and into the sub-granular zone. Also, while Foxc1 controls normal cerebellar and posterior fossa development by regulating 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.

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 significant developmental genes. Disruption of human cerebellar development is often severely handicapping but not lethal, making it amenable to genetic analysis. 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. Human cerebellar malformations have been used to identify cerebellar developmental genes. Gratifyingly, mutations in human RELN cause cerebellar hypoplasia.

Highlighting the genetic bases of known cerebellar disorders;

**-**Here we have, cerebellar vermis hypoplasia (CVH), DWM, Joubert syndrome and related disorders (JSRD), and pontocerebellar hypoplasia (PCH). 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 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 inter-peduncular 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.

Also, transcription factors have been implicated in other types of cerebellar malformations e.g; ptf1a and Ascl1, heterozygous loss of the ZIC1 and ZIC4 genes encoding zinc finger transcription factors can cause DWM.

Here are list of genes and suspected cellular processes that have been implicated in human cerebellar malformations;

| **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, NPH P1 , RPGRIP1L and MEM67 | Granule cell proliferation |
| Pontocerebellar hypoplasia (PCH) | CASK , RARS2 , TSEN54, TSEN34, and TSEN2 | Spine development, cell proliferation, tRNA splicing, cellular maintenance. |

**-**The cerebellar ataxias are a group of clinically homogeneous and genetically heterogeneous neurodegenerative disorders, all characterized by progressive atrophy of the cerebellum leading to motor dysfunction, balance problems, speech, and limb and gait ataxia. These include among others, the dominantly inherited spinocerebellar ataxias, recessive cerebellar ataxias such as Friedreich's ataxia, and X-linked cerebellar ataxias.

**In conclusion;** from researches, 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 will facilitate the identification of other causative genes in human cerebellar malformations.