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

**Developmental Genetics of the Forebrain**

The cerebellum lies in the posterior cranial fossa, it is a highly ordered brain structure related to motor functions with several distinct types of cells. 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 cerbellar anlage. Then, cohorts of differentiated projection neurons and interneuron progenitors migrate into 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. (pubmed. gov)

**Genetic Bases of Known Cerebellar Disorders**

**A**. **Cerebellar Ataxia**

The cerebellar ataxias are a group of clinically homogeneous and genetically heterogeneous neurodegenerative disorders, all characterized by progressive atrophy of the cerebellum and a clear loss of Purkinje cells, leading to impairment of motor function, balance, gait and speech. The most prominent clinical feature is cerebellar ataxia, which is often associated with additional neurological manifestations such as pyramidal, extrapyramidal and cognitive dysfunction. The disease inheritance patterns can be autosomal dominant, recessive, X-linked or even mitochondrial in a few ataxia syndromes. The precise number of cerebellar ataxias is unknown, but at least 37 dominantly inherited spinocerebellar ataxias (SCAs), 20 recessive ataxias and a few X-linked and mitochondrial inherited forms of cerebellar ataxia are known. Despite all the known disease-causing genes, around 30% of all cerebellar ataxia patients remain genetically undiagnosed.

In addition to a genetically heterogeneous background, a broad range of mutation types have been identified that contribute to the complex etiology of the cerebellar ataxias. A large number are caused by coding polyglutamine (CAG; polyQ) repeat expansions, or non-coding CTG, CAG, and GAA repeats, but cerebellar ataxias caused by penta- or hexanucleotide repeat expansions have also been reported. Missense mutations, deletions, duplications, splice and truncating mutations have also been identified. All ataxia genes in dominant cerebellar ataxias seem functionally different but operate in shared pathways including protein misfolding and aggregation, impairment of the protein quality control system, dysregulation of gene transcription, RNA toxicity, and alterations in synaptic transmission. On the other hand, alterations in mitochondrial functioning, DNA repair efficiency, synaptic transmission, chaperone activity, and metabolic functioning underlie recessive cerebellar ataxias. The main challenge for clinicians and researchers is the development of a therapy that can intervene with these various disease mechanisms, as there is no therapy that slows progression or prevents these diseases from occurring.

### B. Dandy-Walker Syndrome Dandy-Walker syndrome (DWS) is a congenital brain malformation, characterized by posterior fossa cyst, cystic dilatation of the fourth ventricle, cerebellar vermis dysgenesis, and an upwardly displaced tentorium. Patients often have motor deficits such as delayed motor development, hypotonia and ataxia. About half have mental retardation, and some have hydrocephalus. It has been suggested that heterozygous loss of ZIC1 and ZIC4 is the cause of this disease. Various managements of DWS have been reported from open excision of the cysts to CSF diversion. Ventriculoperitoneal (VP) and cystoperitoneal (CP) shunt insertion are the most common choices in the treatment of DWS.

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| C. Joubert Syndrome Over three decades have passed since Marie Joubert described the original proband for Joubert syndrome, a rare neurological disorder featuring absence of the cerebellar vermis (i.e. midline). Efforts at deciphering the molecular basis for this disease have been complicated by the clinical and genetic heterogeneity as well as extensive phenotypic overlap with other syndromes. However, progress has been made in recent years with the mapping of three genetic loci and the identification of mutations in two genes, AHI1 and NPHP1. These genes encode proteins with some shared functional domains, but their role in brain development is unclear. Clues may come from studies of related syndromes, including Bardet-Biedl syndrome and nephronophthisis, for which all of the encoded proteins localize to primary cilia. The data suggest a tantalizing connection between intraflagellar transport in cilia and brain development. (pubmed.gov) **D. Pontocerebellar Hypoplasia** Pontocerebellar Hypoplasia (PCH) are very rare, inherited progressive neurodegenerative disorders with prenatal onset (for recent review see[[32]](https://embryology.med.unsw.edu.au/embryology/index.php/Neural_-_Cerebellum_Development#cite_note-PMID21749694-32)). The major features are: hypoplasia or atrophy of cerebellum and pons, progressive microcephaly, and variable cerebral involvement. There is a further classification of 7 different subtypes (PCH1-7) and there is prenatal testing for the related inherited mutations.   * **PCH2, PCH4, PCH5** - Mutations in the 3 tRNA splicing endonuclease subunit genes. * **PCH6** - Mutations in the nuclear encoded mitochondrial arginyl- tRNA synthetase gene. * **PCH1** - Mutations in the tRNA splicing endonuclease, the mitochondrial arginyl- tRNA synthetase and the vaccinia related kinase1. |