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 Assignment

1. Developmental genetics of the cerebellum

The cerebellum lies between the cerebrum and brainstem. It is located in the hind brain. It is involved the the control if voluntary and involuntary movement as well as balance.

Development of the cerebellum can be described in four basic stages.

In the first stage, characterization of cerebellar territory occurs at the midbrain–hindbrain boundary. Transplantation studies in chicken and mouse have found that the isthmus organizer (IsO), a region corresponding to the midbrain–hindbrain boundary expression, is crucial for specifying midbrain and cerebellar structures. At the isthmus, restricted expression of secreted factors, such as fibroblast growth factor 8, FGF8 and Wnt1, the mammalian homolog of Drosophila wingless gene, as well as homeobox proteins En1 and En2 and paired box genes Pax2 and Pax5 are required for early specification of midbrain and hindbrain structures. In the second stage, two compartments for cell proliferation are formed. Purkinje cells and cells of the deep cerebellar nuclei are generated in the roof of the fourth ventricle, and granule cell precursors, as well as cells of the precerebellar nuclei are formed in the rhombic lip. Development of Purkinje cells is not well understood, but they are known to secrete Sonic hedgehog which regulates proliferation of granule cells. By this time point, granule neuron precursors express a number of markers, Math1, nestin, zipro1/RU49 and Zic genes 1, 2. Purkinje cells migrate radially to their final positions, whereas granule neurons migrate over the surface of the developing cerebellum, forming the external granule layer (EGL). In the third stage, cells of the EGL migrate inward along the processes of Bergman glia to their final position in the internal granular layer (IGL). Finally, cerebellar circuitry is established and further differentiation occurs. The lower portion of the rhombic lip also gives rise to cells of the precerebellar nuclei such as the inferior olivary nuclei, which migrate to positions in the brainstem.

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. Given the clear overlap in disease phenotypes and the various modes of presentation of cerebellar ataxia, making a correct diagnosis is challenging. 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. Taken together, all ataxias have an estimated prevalence of 15–20:100,000. 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

Overview of all cerebellar ataxias used in this review.

| Disease | Gene | Mutation type |  |
| --- | --- | --- | --- |
| Conventional mutations |
| SCA5 | SPTBN2 | Missense |  |
| SCA19/22 | KCND3 | Missense/in frame deletion |  |
| SCA28 | ALG3L2 | Missense |  |
| SCA35 | TGM6 | Missense |  |
| SCA26 | eEF2 | Missense |  |
| Adult-onset, recessive spinocerebellar ataxia with psychomotor retardation | SYT14 | Missense |  |
| Early-onset cerebellar neurodegeneration | UCHL1 | Missense |  |
| Recessive cerebellar ataxia with spasticity | GBA2 | Missense |  |
| X-linked cerebellar ataxia | PMCA3 | Missense |  |
| X-linked cerebellar ataxia | GJB1 | Missense |  |
| Cerebellar neurodegeneration and ataxia in mice | RNU2 | Missense |  |
|  |
| Polyglutamine repeat expansions |
| SCA1 | ATXN1 | CAG expansion |  |
| SCA2 | ATXN2 | CAG expansion |  |
| SCA3 | ATXN3 | CAG expansion |  |
| SCA7 | ATXN7 | CAG expansion |  |
| SCA17 | TBP | CAG expansion |  |
|  |
| GAA repeat expansion |
| Friedreich's ataxia | FXN | GAA expansion |  |
|  |  |  |

VLDLR-associated cerebellar hypoplasia is an inherited condition that affects the development of the brain. People with this condition have an unusually small and underdeveloped cerebellum, which is the part of the brain that coordinates movement.

 features of VLDLR-associated cerebellar hypoplasia include moderate to profound intellectual disability, impaired speech (dysarthria) or a lack of speech, and eyes that do not look in the same direction (strabismus). As its name suggests, VLDLR-associated cerebellar hypoplasia results from mutations in the VLDLR gene. This gene provides instructions for making a protein called a very low density lipoprotein (VLDL) receptor. Starting before birth, this protein plays a critical role in guiding the movement of developing nerve cells to their appropriate locations in the brain. Mutations in the VLDLR gene prevent cells from producing any functional VLDL receptor protein. Without this protein, developing nerve cells cannot reach the parts of the brain where they are needed. The resulting problems with brain development lead to ataxia and the other major features of this condition.

X-linked disorders with cerebellar dysgenesis (XLCD) are a genetically heterogeneous and clinically variable group of disorders in which the hallmark is a cerebellar defect (hypoplasia, atrophy or dysplasia) visible on brain imaging, caused by gene mutations or genomic imbalances on the X-chromosome. The neurological features of XLCD include hypotonia, developmental delay, intellectual disability, ataxia and/or other cerebellar signs. Normal cognitive development has also been reported. Cerebellar dysgenesis may be isolated or associated with other brain malformations or multiorgan involvement. There are at least 15 genes on the X-chromosome that have been constantly or occasionally associated with a pathological cerebellar phenotype. 8 XLCD loci have been mapped and several families with X-linked inheritance have been reported. Recently, two recurrent duplication syndromes in Xq28 have been associated with cerebellar hypoplasia. Given the report of several forms of XLCD and the excess of males with ataxia, this group of conditions is probably underestimated and families of patients with neuroradiological and clinical evidence of a cerebellar disorder should be counseled for high risk of X-linked inheritance.

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. 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. While Ophn1 is required for the stabilization of glutamatergic spines, 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. 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. 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. 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. Although mouse Cask mutants have cerebellar hypoplasia, the developmental basis for this pathology has not yet been studied. 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. Individuals with PCH have also been found to have mutations in TSEN54, TSEN34, and TSEN2, which all encode tRNA splicing proteins. 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.

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