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DEVELOPMENTAL GENETICS OF THE CEREBELLUM AND GENETIC BASES OF KNOWN CEREBELLAR DISORDERS.

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.

Genetics has recently enabled the identification of genes causing human pontocerebellar hypoplasia, Joubert syndrome, and Dandy–Walker malformation (DWM). When combined with studies in mouse, a variety of molecular mechanisms, including transcriptional regulation, mitochondrial function, and ciliary signaling have been implicated in homeostasis, patterning, and cell proliferation during cerebellar development. Concurrently, the application of new genomic techniques, which amass vast amounts of biological information, is just beginning to unravel the systems biology of the developing cerebellum.

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 behaviour are also recognised that are all subserved 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 tumours.

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. 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 .

In humans, the cerebellum develops from the dorsal region of the posterior neural tube, and its cells arise from two germinal matrices. Most cells are derived from the ventricular zone, but the granule neurons come from a specialized germinal matrix called the rhombic lip.

The mesencephalon and metencephalon both contribute to the developing mouse cerebellum. The patterning of these two regions depends on signals from the isthmus organizer (IO), located just caudal to their junction. Otx2 and Gbx2are central to IO development. Otx2 is expressed in the mesencephalon, with a posterior boundary at the rostral metencephalon; Gbx2 is expressed in the metencephalon, and its anterior boundary abuts the Otx2 boundary. Reciprocal repression maintains a sharp boundary between these domains. Otx2and Gbx2 form part of a regulatory loop that includes Wnt1, En1 and Fgf8. Many other genes, including members of the Pax and Hox families, are also involved in patterning this region.

The rhombic lip, located between the fourth ventricle and the metencephalic roof plate, gives rise to granule neurons. Proliferation in its germinal epithelium is governed by the Math1 gene. Rhombic lip cells migrate to the cerebellar anlage and settle on its periphery to form the external granule layer, another zone of proliferation. As the cells begin to migrate, they express markers that include RU49/Zipro1, Zic1 and Zic3. RU49/Zipro1 and Zic1 are thought to be involved in cell proliferation, which requires interaction with PCs. PCs might release a diffusible factor such as sonic hedgehog (Shh), and Zic1 could control cell proliferation by indirectly regulating the Shh pathway. The final stage of granule neuron maturation occurs after precursor cell migration into the inner granule layer.

Many genes, including En1, En2, Pax2, Wnt7b, and some of the ephrins and their receptors, show characteristic patterns of spatial expression in the cerebellum, but only En2 has been studied specifically for its role in compartmentalization. In addition to the patterning genes, several other gene families, such as the heat shock proteins and proteins involved in neuronal migration, are also expressed in specific patterns. Spatial- and temporal-specific knockout strategies should yield more information about the roles of these genes in patterning the cerebellum.

GENETIC BASES OF KNOWN CEREBELLAR DISORDERS

The cerebellum plays a main role in motor control and also in cognition features such as attention. Thus, a disturbance in cerebellar development results in neurological disorders such as attention deficit hyperactivity disorder (ADHD), congenital ataxia, and autism.

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. Joubert syndrome is an autosomal-recessive disorder characterized by cerebellar hypoplasia, hypotonia, developmental delay, abnormal respiratory patterns, and abnormal eye movements.

Here we will discuss 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 is also relatively common and often confused with DWM, making estimations of incidence problematic. 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 interpeduncular 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.

Transcription factors have also been implicated in other types of cerebellar malformations. Heterozygous loss of the ZIC1 and ZIC4 genes encoding zinc finger transcription factors can cause DWM, a phenotype which is mimicked in Zic1 and Zic4 double heterozygous mutant mice . Mutations in FOXC1, a transcription factor gene located in the locus, have recently been shown to contribute to human DWM.

Studies of JSRD patients have also provided surprising insights into new developmental mechanisms. Of the nine loci linked to JSRD, eight have been cloned and the following causative genes identified: AHI1 , ARL13B, CC2D2A , CEP290 , INPP5E , NPHP1 , RPGRIP1L , and TMEM67 . Many of these genes are implicated in normal ciliary function and their protein products localize to

the cilia or basal bodies. One such cilia-related protein is Nephrocystin, the product of NPHP1, which interacts with beta-tubulin and localizes to primary cilia. In cell culture, CEP290, centrosomal protein 290, is involved in ciliogenesis, localizes to centrioles in a microtubule-dependent manner, and regulates the microtubule network, as shown through RNAi. Furthermore, CEP290 interacts with the protein product of CCD2A both genetically and physically . Most recently, mutations in the INPP5E gene, which codes for inositol polyphosphate-5-phosphatase E, were found in patients with Joubert syndrome. While it was known that this enzyme hydrolyzes phosphatidylinositols, INPP5E was found to be localized to cilia and mutations resulted in premature destabilization of cilia after stimulation .

Thus, examination of human patients led to a novel role for INPP5E in both cilia signaling and Joubert syndrome. 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.

IIndividuals with PCH have also been found to have mutations in TSEN54, TSEN34, and TSEN2, which all encode tRNA splicing proteins.

JSRD- Joubert Syndrome and Related Disorders
DWM- Dandy-Walker Malformation
CVH- Cerebellar vermis hypoplasia
PCH- Pontocerebellar Hypoplasia

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921561/

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