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ANA 303 Assignment: - Cerebellum and Its Connections.

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Developmental genetics of the cerebellum and the basis of known cerebellar disorders.

The Cerebellum or the small Brain lies in the posterior cranial fossa. It is part of the hind brain (Rhombencephalon). It represents approximately 10 percent of the total volume of the brain. The function is to coordinate muscle movements and maintain posture and balance.

It is one of the first structures of the brain to begin to differentiate and one of the last to mature. Even after birth, it continues to grow for some months.

The cerebellum in humans develops from the dorsal region of the posterior neural tube with its cells originating from two germinal matrices, it arises from two rhombomeres located in the alar plate of the neural tube. The specific rhombomeres from which the cerebellum forms are rhombomere 1 (Rh.1) and the "isthmus". The Cerebellar neurons arise from two primary regions. The first region is the ventricular zone, a place in the roof of the fourth ventricle. It produces the Purkinje cells and deep nuclear neuron of the Cerebellum. The second germinal zone is known as the Rhombic lip. This layer of cells found on the exterior of the cerebellum—produces the granule neurons. The granule neurons migrate from this exterior layer to form an inner layer known as the internal granule layer. The external granular layer ceases to exist in the mature cerebellum, leaving only granule cells in the internal granule layer.

The key transcription factors Math1 and Pax6 are expressed in Rhombic lip (RL) and the external germinal layer (EGL). This means

that Math 1 is essential for the genesis of the granule cells. Ptf1a is expressed in the ventricular neuroepithelium. Cerebellar granule cells go through several epochs of development from their origins in the rhombic lip around E12.5 to the trans-migratory cells that establish the EGL, to the highly proliferative and then migratory population that produces the largest cohort of neurons in the brain.

Cerebellar disorders is a statement used to refer to problems of the Cerebellum, an area in the brain that controls balance and coordination.

Overview of human cerebellar development

The cerebellum develops from the dorsal region of the posterior neural tube. The embryonic cerebellum begins as little more than symmetric bulges into the early fourth ventricle: cerebellar hemispheres arise as mere buds from laminae on either side of the rhombencephalic midline, and the most rostral segment of the metencephalon produces outgrowths that form the first elements of the cerebellum. These lateral elements develop towards the midline and fuse in a rostral-to-caudal direction. As the primitive hemispheres come into contact with each other, they form first the superior and then the inferior vermis. The lateral elements from this fusion develop into the cerebellar hemispheres.

Cells in the cerebellum arise from two different germinal matrices. From the ventricular zone (also known as the ventricular germinal matrix), cells radiate laterally and evolve into the deep cerebellar nuclei and Purkinje cells of the cerebellar cortex. The first cells to be born become the deep cerebellar nuclei at about week eight in human embryogenesis. At week nine, the ventricular zone begins to produce cells that will eventually form the Purkinje neurons. By 24 weeks, these proto-Purkinje cells send dendrites to the PARALLEL FIBRES of the granule neurons. The full number of Purkinje cells is present early on, but their mature monolayer forms sometime between 16 and 28 weeks postnatally. Purkinje cells continue their maturation after

birth, projecting to the deep cerebellar nuclei and refining the input they receive from the CLIMBING FIBRES of inferior olivary neurons.

From the ventricular zone, a third population of neurons is born after the formation of Purkinje cells. These neurons include the stellate, basket and Golgi interneurons that can be found in the molecular layer. These three kinds of neurons have a modulatory action on the Purkinje cells and granule neurons.

Unlike most of the cell types of the cerebellum, which are born at the ventricular zone, cerebellar granule neurons come from a specialized germinal matrix called the rhombic lip. Migration of these primitive cells over the surface of the cerebellum starts as early as week 11 in humans; neuronal elements are present in the external granular layer (EGL) by week 27. From the EGL, a second zone of proliferation, the granule neuron precursors, migrate deeper into the cortex. This inward migration continues after birth, with the EGL disappearing within the first year of life in humans.

In the past decade, genetic studies of various mouse mutants became the primary source of information about cerebellar development

Table 1 Genes involved in various stages of cerebellar development

Table 1 | **Genes involved in various stages of cerebellar development**

Stages/areas of development	Genes, proteins and molecules
Cerebellar primordium	*Otx2, Gbx2, Fgf8, Wnt1, En1/2, Pax2/5,* Bmps, *Shh, Hoxa2*
Granule cell generation	*Math1, RU49/Zipro1, Zic1,2,3, Shh* pathway, *Ccnd2, p27, Neurod1, NSCL1*
Granule cell migration	Tag1, Tuj1, *Pax6,* Dcc/netrin pathway, *Unc5h2,3* GIRK2, astrotactin, thrombospondin, tenascin, neuregulin
Purkinje cell maintenance	Ngf, BDNF, ciliary neurotrophic factor, acetylcholine, Nt4/5, Rorα
Purkinje cell migration	Reelin pathway

BDNF, brain-derived neurotrophic factor; Bmps, bone morphogenetic proteins; *Ccnd2*, cyclin D2; Dcc, deleted in colorectal carcinoma; *En1,2*, engrailed 1,2; *Fgf8*, fibroblast growth factor 8; *Gbx2*, gastrulation brain homeobox 2; *Hoxa2*, homeobox A2; *Math1*, atonal homologue 1 (*Drosophila*); *Neurod1*, neurogenic differentiation 1; Ngf, nerve growth factor; *NSCL1*, nescient helix–loop–helix 1; Nt4,5, neurotrophin 4,5; *Otx2*, orthodenticle homologue 2 (*Drosophila*); *Pax2,5,6*, paired box gene 2,5,6; *p27*, cyclin-dependent kinase inhibitor 1B; Rorα, RAR-related orphan receptor α; *RU49*, zinc finger proliferation 1; *Shh*, sonic hedgehog homologue (*Drosophila*); Tag1, transient axonal glycoprotein 1; Tuj1, class 3 β-tubulin; *Unc5h2,3*, unc5 homologue 2,3 (*C. elegans*); *Wnt1*, wingless-related MMTV integration site 1; *Zic1,2,3*, zinc finger protein of the cerebellum 1,2,3.

Genes in the developing cerebellar primordium

The neural tube can be thought of as comprising four different regions during early development. The most anterior portion of the neural tube, the prosencephalon, gives rise to the forebrain. The mesencephalon, just caudal to the prosencephalon, gives rise to the midbrain, whereas hindbrain regions evolve from the metencephalon and myelencephalon. CHICK–QUAIL CHIMAERA experiments have indicated that both the mesencephalon and metencephalon contribute to the developing cerebellum3, 4, and 5.

The proper patterning of the mesencephalon and the metencephalon is dependent on molecular signals released from the ISTHMUS organizer (IO), which is located just caudal to the junction of these two regions Morphologically, this region is marked by a sharp bend of the neural tube. It has been shown in various mouse mutants, as well as in transplant experiments, that the IO is necessary and sufficient for patterning the mid-/hindbrain region from the neural tube. The IO is, in turn, set up by the expression of a complex array of genes. Two, in particular, are central to its development: Otx2 , one of the mouse

homologues of the Drosophila gene orthodenticle , and Gbx2 , a homologue of the Drosophila gene unplugged 6. At embryonic day (E) 7.75, Otx2 is expressed in the mesencephalon, with a posterior boundary at the rostral metencephalon, whereas Gbx2 expression in the metencephalon is bounded anteriorly by the caudal mesencephalon7, 8. The sharp boundary between the expression domains of these two genes reflects their reciprocal repression9, 10 (For a thorough review of mid-/hindbrain patterning

In addition to helping form the IO molecularly, Gbx2 and Otx2 also regulate the expression of Fgf8 (fibroblast growth factor 8); Otx2 negatively regulates Fgf8 expression, whereas Gbx2 maintains it9, 10, and 14. Fgf8 is involved in regulating the various genes expressed in the mid- and hindbrain regions. Mutant mice with a reduced level of Fgf8 expression have a severe patterning defect of the mid-/hindbrain region, which usually affects the cerebellum15.

Fgf8 is a diffusable factor that exerts its action partially by inducing the expression of wingless homologue 1 (Wnt1) through Lim homeobox 1b (Lmx1b) 16, 17. Wnt1, in turn, maintains the expression of Engrailed (En1)18, which then positively regulates Fgf8 expression, completing the feedback regulatory loop6. Mutants of Wnt1, En1 and Lmx1b all show patterning defects in the mid-/hindbrain region19, 20 (R. Johnson, personal communication). Wnt1 and Lmx1b probably exert their influence through the action of En1 (Ref. 18). En2, a paralogue of En1, might also function in mid-/hindbrain patterning. En2 is expressed shortly after En1. Deletion of En2 against a haploinsufficient En1 mutant background was accompanied by a patterning defect in the mid-/hindbrain region more severe than that seen in a single mutant of En1; similarly, deletion of En1 against a haploinsufficient En2 mutant background also leads to an exaggerated phenotype21.

Although the cross-regulation between Wnt1, En1 and Fgf8 is beginning to be understood, several other genes that are not part of this pathway are also

Important in patterning of the mid-/hindbrain region. The paired box genes Pax2 and Pax5 are expressed in the mid-/hindbrain region21. Pax2-null mice never develop a cerebellum or posterior mesencephalon22. Although Pax5 mutants have only a mild phenotype in the mid-/hindbrain region, mice with a Pax5 mutation against a Pax2-sensitized background lack a cerebellum and posterior midbrain23. Pax2 and Pax5 might also be involved in the regulation of En1, Wnt1 and other patterning genes, and together constitute another positive regulatory loop9.

The Hox gene family, which has an active role in patterning the hindbrain, seems to help to restrict the development of metencephalon structures into the myelencephalon. For example, Hoxa2 (homeobox A2), the most anteriorly expressed Hox gene, probably marks the caudal limit of the cerebellar anlage at rhombomere 1 (Ref. 24). Mice without Hoxa2 develop enlarged cerebella24.

Less is known about the dorsoventral patterning in this region. Bone morphogenetic proteins (Bmps) and sonic hedgehog (Shh) govern neuronal fates in the spinal cord; they have also been implicated in dorsoventral patterning of the mid-/hindbrain region. Bmps can induce the cerebellar granule neuron marker mouse atonal homologue 1 (Math1) when expressed in the ventral neural tube of the region25, and ectopic expression of SHH in the chick dorsal neural tube leads to ventralization of the neural tube and disruption of the mid-/hindbrain region26. Cerebellar development is also affected by ectopic expression of Shh, which leads to defects of the midline of the neural tube26.

In sum, the reciprocal repression of Otx2 and Gbx2 forms the IO, which in turn uses Fgf8 and En1 to pattern the prospective mid-/hindbrain region. Cells from both the mesencephalon and the metencephalon give rise to cerebellar tissues.

<u>These disorders include;</u>

1. Dandy-Walker syndrome: A congenital anomaly relating to the Cerebellar Vermis, 4th ventricle and posterior fossa. It is characterized

by an underdevelopment of the Cerebellar vermis, cystic enlargement of the 4th Ventricle and enlargement of the posterior fossa. A distinguishing symptom is Hydrocephalus. The cause for some patients has been as a result of chromosome abnormalities including deletion of chromosome 3q24.3, 6p25 or 13q32.2-q33.2, or duplication of 9p.

2. Cerebellar Hypoplasia: a neurological condition in which the cerebellum is smaller than usual or incompletely developed. It is a feature of a number of congenital malformation syndromes, such as Walker-Warburg syndrome. It is said to be due to a defect in the neuronal proliferation and neuronal migration during the development of the embryonic nervous system. Symptoms in infants may include; problems with walking and balance, seizures, and intellectual disability.

3. Joubert Syndrome: a condition characterized by the absence or underdevelopment of the cerebellar vermis in addition to a malformed brain stem. The most common features of in infants include abnormally rapid breathing, abnormal eye movements, hypotonia, etc. In most cases, Joubert syndrome is inherited in an autosomal recessive manner.

4. Machado-Joseph Disease: an autosomal dominant neurodegenerative disease causing progressive Cerebellar Ataxia, resulting in a lack of motor control and coordination. This disease is a result of a genetic mutation that causes an expansion of abnormal 'CAG' trinucleotide which eventually forms an abnormal form of the protein Ataxin that causes the degeneration of the cells of the hindbrain.

5. Miller-Fisher syndrome: a nerve disorder that relates to the Guillain-Barré syndrome. Often triggered by a viral infection, most commonly the flu, characterized by muscle weakness, paralysis of the eye muscles and absence of tendon reflexes.

Causative Genes in Human Cerebellar Malformations

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 (Table 1).

Cerebellar malformations	Implicated human genes	Likely disrupted process
Cerebellar vermis hypoplasia (CVH)	OPHN1 [59, 60]	Spine morphogenesis
Dandy–Walker malformation (DWM)	ZIC1, ZIC4 [65], FOXC1 [17]	Granule cell differentiation
Joubert syndrome and related disorders (JSRD)	AHI1 [67, 68], ARL13B [69], CCD2A [70, 71], CEP290 [72, 73], INPP5E [74, 75], NPHP1 [76, 77], RPGRIP1L [78, 79], and TMEM67 [80]	Granule cell proliferation
Pontocerebellar hypoplasia (PCH)	CASK [86], RARS2 [88], TSEN54, TSEN34, and TSEN2 [89]	Spine development, cell proliferation, tRNA splicing, cellular maintenance.

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