

17/MHS01/277

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NEUROANATOMY (ANA 303)

QUESTION: WRITE A CONCISE REVIEW ON THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM AND HIGHLIGHT THE GENETIC BASES OF THE KNOWN CEREBELLAR DISORDERS.

ANSWER:

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 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 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. They include:

1. 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.
2. 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, and hypotonia. Etc. In most cases, Joubert syndrome is inherited in an autosomal recessive manner.
3. 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.

4. 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.
5. 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.