NAME: NWAOLISA CHIOMA SUCCESS

MATRIC NUMBER: 17/MHS01/207

COURSE: NEUROANATOMY

COURSE CODE: ANA 303

ASSIGNMENT ON CEREBELLUM AND ITS CONNECTIONS

A concise review on the developmental genetics of the cerebellum and highlight the genetic bases of known cerebellar disorders

ANSWER

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 cerebellar anlage. Then, cohorts of differentiated projection neurons and interneuron progenitors migrate into the 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.

**Genetic bases of known cerebellar disorders**

1. Joubert syndrome (JS): is an autosomal recessive neurodevelopmental disorder, which is characterized by the molar tooth malformation (MTM), a complex brainstem malformation that reflects aplasia or marked hypoplasia of the cerebellar vermis, thickened and elongated superior cerebellar peduncles and a deepened interpeduncular fossa that is apparent on axial MRI at the midbrain–hindbrain junction . Clinically, classic JS is associated with neonatal hypotonia (loss of muscle tone), ataxia, developmental delay, mental retardation, and often neonatal apnea/hyperpnea (irregular breathing) and/or ocular motor apraxia (difficulties in initiating rapid horizontal eye movements—saccades). Autistic features have also been reported as a relatively common component of JS. **mutations in two genes, AHI1 and NPHP1. These genes encode proteins with some shared functional domains.**
2. Dandy-walker’s syndrome: . Dandy-Walker syndrome, sometimes (20-80%), is associated with hydrocephalus, This can cause abnormal high pressure within the skull and head swelling, which can lead to nerve damage. The degree of inability to control muscle coordination is different in the Dandy-Walker syndrome, but is usually life-long. Signs and symptoms of Dandy-Walker syndrome Signs of Dandy-Walker syndrome usually include: delayed growth, muscle weakness (hypotonia), muscle cramps (spasm), poor coordination in balance (imbalance), and enlargement of the circumference of the head and increased internal pressure of the skull due to hydrocephalus in the head. Seizures occur in 15-30% of those affected by Dandy-Walker's syndrome. In addition, respiratory control centers in the brain stem of people with Dandy-Walker syndrome are sometimes damaged, which can lead to respiratory failure in these individuals. The enlargement of the ventricular cysts 4 or enlargement of the posterior cavity of the brain is one of the most prominent features of the Dandy-Walker syndrome. **Dandy-Walker syndrome has a genetic mutations in the genes ZIC1 and ZIC4**
3. Pontocerebellar hypoplasia is a group of related conditions that affect the development of the brain. The term "pontocerebellar" refers to the pons and the cerebellum, which are the brain structures that are most severely affected in many forms of this disorder. Pontocerebellar hypoplasia also causes impaired growth of other parts of the brain, leading to an unusually small head size (microcephaly). This microcephaly is usually not apparent at birth but becomes noticeable as brain growth continues to be slow in infancy and early childhood. The two major forms of pontocerebellar hypoplasia are designated as type 1 (PCH1) and type 2 (PCH2), PCH1 causes problems with muscle movement resulting from a loss of specialized nerve cells called motor neurons in the spinal cord, similar to another genetic disorder known as spinal muscular atrophy. Individuals with PCH1 also have very weak muscle tone (hypotonia), joint deformities called contractures, vision impairment, and breathing and feeding problems that are evident from early infancy. Common features of PCH2 include a lack of voluntary motor skills (such as grasping objects, sitting, or walking), problems with swallowing (dysphagia), and an absence of communication, including speech. Affected children typically develop temporary jitteriness (generalized clonus) in early infancy, abnormal patterns of movement described as chorea or dystonia, and stiffness (spasticity). Many also have impaired vision and seizure**s. Pontocerebellar hypoplasia can result from mutations in several genes. About half of all cases of PCH1 are caused by mutations in the EXOSC3 gene. PCH1 can also result from mutations in several other genes, including TSEN54, RARS2, and VRK1. PCH2 is caused by mutations in the TSEN54, TSEN2, TSEN34, or SEPSECS gene. In addition to causing PCH1 and PCH2, mutations in the TSEN54 gene can cause PCH4 and PCH5. Mutations in the RARS2 gene, in addition to causing PCH1, can result in PCH6.**

REFERENCE

Shahin Asadi., et al. “Study of Genetics Mutations ZIC1, ZIC2 and ZIC4 Genes in Dandy-Walker Syndrome Human 2018 ”. Current Opinions in Neurological Science 2.2 (2018): 445-455