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QUESTION

Write a concise review on the developmental genetics of the cerebellum and highlight the genetic bases of known cerebellar disorder.

ANSWER

The cerebellum is crucial for controlling movement; it is also implicated in higher order function such as cognition and is derived from the dorsal rhombomere 1 which comprises of the most anterior aspect of the hindbrain. Expression of the homeobox genes Otx2 and Gbx2 are essential for the development of the midbrain and hindbrain. During development these two genes are expressed in abutting domains where they antagonize each other to establish the mid/hind brain boundary and formation of an isthmic organizer (IsO). The IsO functions as a classic signalling centre by secreting fibroblast growth factor 8 (FGF8), which maintains the posterior border of Otx2 expression and is crucial for normal cerebellar development. The IsO is located just caudal to the junction of the metencephalon and mesencephalon and is also necessary and sufficient for patterning of the midbrain and hind brain. FGF expression will result in the absence of midbrain and cerebellum. It is also required for cell survival. A number of other genes cooperate with FGF8 to control cerebellar development and they are the homeobox genes En1 and En2 (engrailed) and paired box genes Pax2 and Pax5. Pax2 induces FGF8 while En1 and En2 are necessary for its maintenance.

Cerebellar cells are born and migrate from two germinal zones: the ventricular zone that produces inhibiting GABAergic neurons and rhombic lip generates glutamatergic neurons. The cells derived these zones are produced from multipotent radial glial progenitor cells is reliant on wingless (WNT) signalling. Thereafter, it requires the expression of the sonic hedgehog (SHH) gene. Sonic hedgehog gene is first delivered to the cerebellum by the cerebrospinal fluid in the fourth ventricle, then is secreted later by purkinjie cells and plays a key role in proliferation of granule cell precursors. Cellular fate in cerebellum is determined by the differential expression of genes that encode key transcription factors. Studies shown GABAergic neurons are derived from progenitors that express ptfa1 and Atonal homolog 1 (Atoh1) formerly known as Math1. Ptfa1 and Atoh1 are said to contribute to the general identities of inhibitory and excitatory cells in the cerebellum. Formation of purkinijie cell stripes are said to be dependent on early b-cell factor 2 (EBF2) and homeodomain transcription factors En1/2. En1 and En2 play critical roles in patterning stripped gene expression. En1/2 regulates the targeting of mossy fibres to subsets of cerebellar lobules showing a main role for afferent topography. The RORA (Retinoic acid related orphan receptor alpha) gene plays a pivotal role in development of the cerebellum. Its functions extend beyond development for instance it protects the neurons against oxidative stress and shows anti-inflammatory action by inhibition of the NF-Kappa pathway.

Foliation is said to be under genetic control from purkinjie cell derived sonic hedgehog (SHH) signals through the GLI2 transcription factor to control granule cell precursor proliferation which is required for foliation. However En2 appears to play a more specific role than SHH. It also controls the patterning of hemisphere morphology of the cerebellum.

CEREBELLAR DISORDERS AND THEIR GENETIC BASES

1. **ATAXIA-TELANGIECTASIA**

   Ataxia-telangiectasia is a rare inherited disorder that affects the nervous system, immune system, and other body systems. This disorder is characterized by progressive difficulty with coordinating movements (ataxia) beginning in early childhood, usually before age 5. Affected children typically develop difficulty walking, problems with balance and hand coordination, involuntary jerking movements (chorea), muscle twitches (myoclonus), and disturbances in nerve function (neuropathy). Mutations in the ATM gene cause ataxia telangiectasia. The ATM gene provides instructions for making a protein that helps control cell division and is involved in DNA repair. This protein plays an important role in the normal development and activity of several body systems, including the nervous system and immune system. Mutations in the ATM gene reduce or eliminate the function of the ATM protein. Without this protein, cells become unstable and die. Cells in the part of the brain involved in coordinating movements (the cerebellum) are particularly affected by loss of the ATM protein. The loss of these brain cells causes some of the movement problems characteristic of ataxia telangiectasia.

2. **FRIEDREICH ATAXIA**

   Friedreich ataxia is a genetic condition that affects the nervous system and causes movement problems. People with this condition develop impaired muscle coordination (ataxia) that worsens over time. Other features of this condition include the gradual loss of strength and sensation in the arms and legs; muscle stiffness (spasticity); and impaired speech, hearing, and vision. Mutations in the FXN gene cause Friedreich ataxia. This gene provides instructions for making a protein called frataxin. Although its role is not fully understood, frataxin is important for the normal function of mitochondria, the energy-producing centres within cells. Certain nerve and muscle cells cannot function properly with a shortage of frataxin, leading to the characteristic signs and symptoms of Friedreich ataxia.

3. **HUNTINGTON DISEASE**

   Huntington disease is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of thinking ability (cognition). Mutations in the HTT gene cause Huntington disease. The HTT gene provides instructions for making a protein called huntingtin. Although the function of this protein is unknown, it appears to play an important role in nerve cells (neurons) in the brain. The HTT mutation that causes Huntington disease involves a DNA segment known as a CAG trinucleotide repeat. This segment is made up of a series of three DNA building blocks (cytosine, adenine, and guanine) that appear multiple times in a row. Normally, the CAG segment is repeated 10 to 35 times within the gene. An abnormal increase in the size of the CAG segment leads to the production of an abnormally long version of the huntingtin protein. The elongated protein is cut into smaller, toxic fragments that bind together and accumulate in neurons, disrupting the normal functions of these cells. The dysfunction and eventual death of neurons in certain areas of the brain underlie the signs and symptoms of Huntington disease

4. **JOUBERT SYNDROME**

Joubert syndrome is a disorder that affects many parts of the body. The signs and symptoms of this condition vary among affected individuals, even among members of the same family. The hallmark feature of Joubert syndrome is a combination of brain abnormalities that together are known as the molar tooth sign, which can be seen on brain imaging studies. This syndrome is associated with mutation of gene encoding components of the primary cilia which is a determinant for sonic hedgehog signal transduction. Disruption of primary cilia formation will block the proliferation of neural progenitors of granule cells mediated by sonic hedgehog gene.

5. **LEIGH SYNDROME**

Leigh syndrome is a severe neurological disorder that usually becomes apparent in the 6rst year of life. This condition is characterized by progressive loss of mental and movement abilities (psychomotor regression) and typically results in death within two to three years, usually due to respiratory failure. Leigh syndrome can be caused by mutations in one of more than 75 different genes. In humans, most genes are found in DNA in the cell's nucleus, called nuclear DNA. However, some genes are found in DNA in specialized structures in the cell called mitochondria. This type of DNA is known as mitochondrial DNA (mtDNA). While most people with Leigh syndrome have a mutation in nuclear DNA, about 20 per cent have a mutation in mtDNA. Most genes associated with Leigh syndrome are involved in the process of energy production in mitochondria. During oxidative phosphorylation, the protein complexes drive the production of adenosine triphosphate (ATP), the cell's main energy source, through a step-by-step transfer of negatively charged particles called electrons. Many of the gene mutations associated with Leigh syndrome affect proteins in these complexes or disrupt their assembly. These mutations reduce or eliminate the activity of one or more of these complexes, which can lead to Leigh syndrome.

6. **LAFORA PROGRESSIVE MYOCLONUS EPILEPSY**

Lafora progressive myoclonus epilepsy is a brain disorder characterized by recurrent seizures (epilepsy) and a decline in intellectual function. Myoclonus is a term used to describe episodes of sudden, involuntary muscle jerking or twitching that can affect part of the body or the entire body. Lafora progressive myoclonus epilepsy can be caused by mutations in either the EPM2A gene or the NHLRC1 gene. These genes provide instructions for making proteins called laforin and malin, respectively. Laforin and malin play a critical role in the survival of nerve cells (neurons) in the brain. Studies suggest that laforin and malin work together and may have several functions. Laforin and malin may prevent a potentially damaging build-up of glycogen in tissues that do not normally store this molecule, such as those of the nervous system. Researchers have discovered that people with Lafora progressive myoclonus epilepsy have distinctive clumps called Lafora bodies within their cells. Lafora bodies are made up of an abnormal form of glycogen that cannot be broken down and used for fuel. Instead, it builds up to form clumps that can damage cells. Neurons appear to be particularly vulnerable to this type of damage. Mutations in the EPM2A gene prevent cells from making functional laforin, while NHLRC1 gene mutations prevent the production of functional malin. It is unclear how a loss of either of these proteins leads to

the formation of Lafora bodies. However, a loss of laforin or malin ultimately results in the death of neurons, which interferes with the brain's normal functions.

REFERENCES

1. WIREs Dev Biol 2012. doi: 10.1002/wdev.65
2. Wang, V. Y. & Zoyhbi, H. Y. (2001). Genetic regulation of cerebellar development. *Nature reviews/ Neuroscience Vol 2.* www.nature.com/reviews/neuro
3. Manto MU & Jissendi P (2012) Cerebellum: links between development, developmental disorders and motor learning. *Front. Neuroanat. 6:1.* doi: 10.3389/fnana.2012.00001
4. www.nlm.nih.gov