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

The cerebellum is derived from dorsal rhombomere, which comprises the most anterior aspect of the hindbrain. .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. 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.

THE ENGRAILED-2 GENE

- The engrailed (En) homebox transcription factor family is critical for the patterning of cerebellar lobules and for Purkinje cells protein stripes.
- The En1/2 regulates the targeting of mossy fiber systems to subsets of cerebellar lobules, showing a main role for the afferent topography in the cerebellar circuitry.
- Initially, the En1/2 mRNA/protein are expressed in the ventricular zone.

- During early post-natal cerebellogenesis, En1/2 are expressed in spatially restricted patterns in most cell types.
- It is plausible that En1/2 are implicated in neurodevelopmental disorders such as autism spectrum disorder.

MATH1

- The specification and differentiation of glutamatergic lineages is dependent upon Math1, a transcription factor of the bHLH (basic helix-loop-helix) class.
- Math1 is critical for the proper development of the granular layer of the cerebellum.
- Math1 null embryos lack interneurons giving rise to the spinocerebellar and cuneocerebellar tracts.

PTF1A AND ASCL1

- Cerebelless mutants have a deficit in the transcription factor Ptf1a (pancreatic transcription factor 1a).
- They show a lack of Purkinje cells and gabanergic interneurons.
- It has been demonstrated that climbing fiber neurons are derived from the Ptf1a domain.
- In Ptf1a null mutants, immature climbing fiber neurons cannot migrate or differentiate, causing a failure in the formation of the inferior olivary nucleus. Ptf1a is also involved in the control of fate and survival of neurons during development.
- In human, mutations of Ptf1a are associated with cerebellar agenesis.
- Ascl1 directs ventricular neuro-epithelium progenitors toward inhibitory interneuron fate and suppresses the astrocytic differentiation.

RORA (RETINOIC-ACID-RELATED ORPHAN RECEPTOR ALPHA) GENE

- Rora is a transcription factor encoding a retinoid-like nuclear receptor which is highly expressed in the cerebellum.
- Rora belongs to the steroid-thyroid hormone receptor superfamily.
- Rora plays a pivotal role in the development of the cerebellum however, its functions extend beyond development.
- For instance, Rora also protects neurons against oxidative stress and shows an anti-inflammatory action by inhibiting the NF-Kappa-B.

REELIN AND CEREBELLAR DEVELOPMENT

- The external granular layer promotes Purkinje cell migration by secreting reelin (RELN), an extracellular matrix component attracting or repealing precursors and axons during development, acting as an extracellular signalling molecule.
- Reelin continues exerting activities beyond birth; it modulates long-term potentiation and is thus involved in learning.
- In the adult brain, Reelin regulates structural and functional properties of synapses.

THE CHEMOKINE RECEPTOR 4 (CXCR4)-CHEMOKINE LIGAND 12 (CXCL12) SYSTEM

- Chemokines and their receptors are determinant in cell migration and in organogenesis.
- Down-regulation of CXCR4 causes an inward radial migration of granule cells precursors.

SONIC HEDGEHOG AND CEREBELLAR DEVELOPMENT

- Sonic hedgehog is highly expressed in the cerebellum.
- Sonic hedgehog is a morphogenetic factor which is a master player in cerebellar patterning and foliation.
- A link between cholesterol metabolism, sonic hedgehog and cerebellar development has been established; indeed, cholesterol deficiencies are associated with defects in the sonic hedgehog signalling (cholesterol is an activator of sonic hedgehog) and cause cerebellar malformations.
- Sonic hedgehog stimulates very strongly the proliferation of cerebellar granular neuronal precursors through the induction and repression of cell cycle regulators genes.
- In addition, sonic hedgehog contributes to cerebellar cortex development by promoting Bergmann glia proliferation and thus contributing to the migration support.

Cerebellar disorders include:

I. Friedreich's ataxia
II. Multiple sclerosis
III. Ataxia telangiectasia
IV. Huntington's disease
V. Progressive myoclonus epilepsy
VI. Leigh syndrome

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 and although its role is not fully understood, frataxin is important for the normal function of mitochondria.
- One region of the FXN gene contains a segment of DNA known as a GAA trinucleotide repeat. This segment is made up of a series of three DNA building blocks (one guanine and two adenines) that appear multiple times in a row.
- Normally, this segment is repeated 5 to 33 times within the FXN gene but in people with Friedreich ataxia, the GAA segment is repeated 66 to more than 1,000 times.

- The length of the GAA trinucleotide repeat appears to be related to the age at which the symptoms of Friedreich ataxia appear, how severe they are, and how quickly they progress.
- The abnormally long GAA trinucleotide repeat disrupts the production of frataxin, which severely reduces the amount of this protein in cells leading to the characteristic signs and symptoms of Friedreich ataxia.

MULTIPLE SCLEROSIS (MS)

- MS is a potentially disabling disease of the brain and spinal cord.
- In MS, the immune system attacks the myelin that covers nerve fibers and causes communication problems between the brain and the rest of the body.
- Changes in the HLA-DRB1 gene are the strongest genetic risk factors for developing multiple sclerosis.
- The HLA-DRB1 gene belongs to a family of genes called the human leukocyte antigen (HLA) complex which helps the immune system distinguish the body's own proteins from proteins made by foreign invaders (such as viruses and bacteria).
- Variations in several HLA genes have been associated with MS risk, but one particular variant of the HLA-DRB1 gene, called HLADRB1*15:01, is the most strongly linked genetic factor.
- Other factors associated with an increased risk of developing MS include changes in the IL7R gene and environmental factors, such as exposure to the Epstein-Barr virus, low levels of vitamin D, and smoking.

ATAXIA TELANGIECTASIA

- 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.
- The ATM protein assists cells in recognizing damaged or broken DNA strands and coordinates DNA repair by activating enzymes that fix the broken strands.
- Mutations in the ATM gene reduce or eliminate the function of the ATM protein and without this protein, cells become unstable and die.
- Cells in the cerebellum are particularly affected by loss of the ATM protein as the loss of these brain cells causes some of the movement problems characteristic of ataxia telangiectasia.
- Mutations in the ATM gene also prevent cells from responding correctly to DNA damage, which allows breaks in DNA strands to accumulate and can lead to the formation of cancerous tumours.

HUNTINGTON'S 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 and 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 (cytosine, adenine, and guanine) trinucleotide repeat.
- Normally, the CAG segment is repeated 10 to 35 times within the gene however, in people with Huntington disease, the CAG segment is repeated 36 to more than 120 times.
- People with 36 to 39 CAG repeats may or may not develop the signs and symptoms of Huntington disease, while people with 40 or more repeats almost always develop the disorder.
- An 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.

PROGRESSIVE MYOCLONUS EPILEPSY

- Progressive myoclonus epilepsy is a brain disorder characterized by recurrent seizures (epilepsy) and a decline in intellectual function.
- The signs and symptoms of the disorder usually appear in late childhood or adolescence and worsen with time.
- 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; one of these is to help regulate the production of glycogen, which is a major source of stored energy in the body.
- 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.
- Mutations in the EPM2A gene prevent cells from making functional laforin, while NHLRC1 gene mutations prevent the production of functional malin.
- Loss of laforin or malin ultimately results in the death of neurons, which interferes with the brain's normal functions.
- The condition tends to progress more slowly in some people with NHLRC1 gene mutations than in those with EPM2A gene mutations.

LEIGH SYNDROME

- Leigh syndrome is a severe neurological disorder that usually becomes apparent in the 6th 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 and while most people with Leigh syndrome have a mutation in nuclear DNA, about 20 percent have a mutation in mitochondrial DNA.
- Most genes associated with Leigh syndrome are involved in the process of energy production in mitochondria.
- Mitochondria use oxygen to convert the energy from food into a form cells can use through a process called oxidative phosphorylation and five protein complexes are involved in this process; complex I, complex II, complex III, complex IV, and complex V.
- Disruption of complex I, also called NADH: ubiquinone oxidoreductase, is the most common cause of Leigh syndrome, accounting for nearly one third of cases of the condition.
- At least 25 genes involved in the formation of complex I, found in either nuclear or mitochondrial DNA, have been associated with Leigh syndrome.
- Disruption of complex IV, also called cytochrome-c oxidase or COX, is also a common cause of Leigh syndrome, underlying approximately 15 percent of cases.
- One of the most frequently mutated genes in Leigh syndrome is SURF1.
- This gene, which is found in nuclear DNA, provides instructions for making a protein that helps assemble the COX protein complex (complex IV).
- Mutations in the SURF1 gene typically lead to an abnormally short SURF1 protein that is broken down in cells, resulting in the absence of functional SURF1 protein.
- The most common mitochondrial DNA mutation in Leigh syndrome affects the MT-ATP6 gene, which provides instructions for making a piece of complex V, also known as the ATP synthase protein complex.
- MT-ATP6 gene mutations, found in approximately 10 percent of people with Leigh syndrome, block the generation of ATP.