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Question: **Write a concise review on the development genetics of the cerebellum and highlight the genetics bases of known cerebellar disorders**.

Answer

Development genetics is the study of how gens control the growth and development of an organism throughout its life cycle.

The cerebellum is one of the first brain structures to begin to differentiate yet it is one of the last to achieve maturity. The cerebellum acts as a co-ordination center, using sensory inputs from the periphery to fine tune our movement and balance.

Genes involved in the development of cerebellar primordium

Chick-Quail Chimera experiments have indicated that both the mesencephalon and metencephalon contribute to the development of cerebellum. Proper patterning of the mesencephalon and metencephalon is dependent on molecular signals released from the Isthmus Organizer (IO), which is located just caudal to the junction of these two regions. The IO in turn is set up by the expression of a complex array of genes, Otx2 and Gbx2.

At embryonic day, 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 mesencephalon. In addition to help form the IO molecularly, Gbx2 and Otx2 regulate the expression of Fgf8 (fibroblast growth factor 8).

Otx2 negatively regulates Fgf8 expression, whereas Gbx2 maintains it. The Fgf8 is involved in regulating the various genes expressed in mid and hind brain regions.

Fgf8 is a diffusible factor that exerts its action partially by inducing the expression of wingless homologue 1 (Wnt1) through Lim homeobox 16 (Lmx16). Wnt 1 in turn maintains the expression of engrailed (En1), which then positively regulates Fgf8 expression, completing the feedback regulatory loop. Mutants of Wnt1 and En1 andLmx16 all show patterning defects in mid or hind brain region.

The genes Pax 2 and Pax 5 are expressed in the mid/hind brain region also. Pax 2 and Pax 5 might also be involved in the regulation of En 1, Wnt 1 and other patterning genes and together constitute another positive regulatory loop. Bone morphogenetic protein and sonic hedgehog are involved in dorsoventral patterning of the mid/hind brain regions.

In summary, the reciprocal repression of Otx2 and Gbx2 forms the IO which in turn uses Fgf8 and En1 to pattern the prospective mid/hind brain region.

Development of the purkinje cells

The Purkinje, Golgi, stellate and basket cells all arise from the ventricular neuroepithelium. Purkinje cells are born at embryonic day 13 and they begin to express the calcium-binding protein **Calbindin**. These purkinje cells become suspended beneath the external granular layer, awaiting the inward migration of granule neurons. The timely arrest of migration is dependent on the **reelin pathway**.

In late embryogenesis, climbing fibers from the inferior olivary nucleus start to innervate purkinje cells. This interaction is believed to influence Purkinje cell development. Wnt genes are involved in axon and dendrite development and the Wnt3 gene is expressed in purkinje cells during axon and dendrite development and its expression is dependent on granule neurons.

The Rorα (RAR-related orphan receptor α) genes is important for the survival of purkinje cells.

Development of Rhombic lip and Granule neurons

Granule neurons develop from a separate germinal epithelium known as the rhombic lip. The rhombic lip is located between the 4^{th} ventricle and the roof

plate of the metencephalon. Expression of the Math1 gene (which is expressed on the mid/hind brain region as early as embryonic day 9), governs the germinal epithelium of the rhombic lip.

In chick-quail chimera experiments, it has shown that the rhombomere 1 region of the rhombic lip is the probable source of granule neuron precursors which eventually gives rise to the granule neuron. Purkinje cells release a diffusible factor, sonic hedgehog (shh) which control proliferation of the granule neuron precursors. Zic proteins proteins have been shown to modulate the activity of the Gli protein which in turn mediate Shh function.

Cyclin D2 is important in cerebellar granule neuron proliferation and in the final maturation of granule neurons the gene Wnt7a (that is in the dendrites and axon formation).

The rhombic lip also generates cells in the pontine nucleus, external cuneate nucleus, lateral reticular nucleus, reticulotegemental nucles (which supplies mossy fibres to granule cells.

Some cerebellar disorder with their Genetic bases

1) Joubert Syndrome: This is a congenital brain malformation of the cerebellar vermis and brainstem with abnormalities of axonal decussation affecting the corticospinal tract and superior cerebellar peduncle. This is autosomal recessive disorder characterized by partial or complete agenesis of cerebellar vermis.

Mutations in 2 genes result in this syndrome, these genes encodes proteins with some shared functional domains, but the role in brain development is unclear:

- **AHI 1**, which is highly expressed in brain particularly in neuron that giverise to crossing axon of the corticospinal tact and superior cerebellar peduncle.
- **NPHP 1**

Individuals with this syndrome have motor and behavioral abnormalities, including an inability to walk due to severe clumsiness and mirror movements and cognitive and behavioral disturbances.

2) Leigh Syndrome: This is a severe neurological disorder that usually becomes apparent in the year of life and it is commonly inherited in an autosomal recessive pattern. This condition is characterized by progressive loss of mental and movement abilities. Affected individuals may develop weak muscle tone (hypotonia), involuntary muscle contractions (dystonia) and problems with movement and balance, these is also loss of sensation and weakness of limbs.

Leigh syndrome can be caused by mutations in one or more genes and most of these genes are involved in the process of energy production in mitochondria, which disrupt their assembly. These genes are:

- The **SURF1 gene**: this gene is found in nuclear DNA and when mutated lead to an abnormally short SURF1 protein that is broken down in cells, resulting in the mitochondrial energy production.
- MT-ATP6 gene: Mutation in this mitochondrial DNA gene block the generation of ATP.

3) Ataxia-telangiectasia: This is a rare inherited disorder that affects the nervous system, immune system and other body systems. Affected children typically develop difficulty walking, problems with balance and hand co-ordination, involuntary jerking movements (chorea), muscle twitches (myoclonus) and disturbances in nerve function (neuropathy).

Mutations in the **ATM gene** (which provides instructions for making an ATM protein that helps control cell division and is involved in DNA repair), cause Ataxia-telangiextasia.

4) Friedreich Ataxia: people with this condition develop impaired muscle co-ordination (ataxia) that worsens over time. Gradual loss of strength and sensation in the arms and legs, muscle stiffness (spasticity) and impaired speech, hearing and vision. Some affect individuals that develop diabetes.

Mutations in the **FXN gene** causes this condition. This gene provides instructions for making a protein called Frataxin.

5) Basal cell Naevus Syndrome: patients with this syndrome have Medulloblastoma (a tumor of the granule cell precursor origin that affects children).

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