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MATRIC NUMBER: 17/MHS01/216

DEPARTMENT: MEDICINE AND SURGERY

COURSE CODE: ANA 303

COURSE TITLE: NEUROANATOMY

QUESTION

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

The major features of cerebellar development include, the neuronal populations which are generated in a sequential manner, the inhibitory interneurons which emerge from the ventricular zone and glutamatergic neurons which, are generated by the rhombic lip. They are also linked to genetic development. The genes involved in the development of the cerebellum include; the engrailed-2 gene, math1, ptf1a and ascl1, retinoic-acid-related orphan receptor alpha gene (RORA) and sonic headhog.

The sonic headhog is highly expressed in the cerebellum. It is a master player in cerebellar patterning and foliation. The sonic headhog controls proliferation of progenitors in the cerebellum through the induction and repression of cell cycle regulator genes. A link between sonic headhog, cholesterol metabolism and cerebellar development is formed when it binds to the transmembrane receptor. Defect in the signaling of this gene causes cerebellar malformations like hypoplasia of the cerebellum. The hypoplasia of the cerebellum is due to defects in cholesterol homeostasis which, is linked to poor signaling of the sonic headhog.

The RORA is a transcription factor that encodes retinoid like nuclear receptor that is highly expressed in the cerebellum. The gene plays a pivotal role in the development of the cerebellum. Its mutation is associated with severe degeneration of purkinje neurons and a nearly total absence of granule cells at the end of first postnatal month. The homozygous RORA is highly ataxic and the heterozygous RORA appears phenotypically normal only showing disabilities during challenging tasks.

The climbing fibers have been demonstrated to be derived from the Ptf1a domain. This gene is also involved in the control of fate and survival of neurons during the development. Mutation of Ptf1a in human is associated with cerebellar agenesis. They show a lack of purkinje cells and gabanergic interneurons. In Ptf1a null mutants, immature climbing fibers cannot migrate hence, causing failure in the formation of the inferior olivary nucleus.

Math1 is a transcription factor of the bHLH class. It controls the specification and differentiation of glutamatergic lineages. It is important for the proper development of the granular layer of the cerebellum.

The engrailed homebox transcription factor family is important for the patterning of cerebellar lobules and for purkinje cells protein stripes. The En1/2 regulates the targeting mossy fiber systems to subsets of cerebellar lobules, showing a main role for afferent topography in cerebellar circuitry. In neurodevelopment disorders like, autism spectrum disorder, En1/2 is implicated.

**REFERENCES**

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