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Course: Neuroanatomy: Cerebellum and its Connections

**300 level MBBS**

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**Question: Write a concise review on the developmental genetics of the cerebellum and highlight the genetic basis of known cerebellar disorders.**

**Introduction**

The cerebellum is the second largest part of the brain located inferior to the cerebrum and posterior to the brain stem. Although the cerebellum is crucial for controlling movement, it is also implicated in higher order function such as cognition. Accordingly, its contribution to disease likely extends beyond the ataxias to include autism spectrum disorders and schizophrenia. Its potential involvement in developmental and adult onset diseases and its well-understood circuitry make the cerebellum an attractive model for investigating the mechanistic underpinnings and embryonic origins of brain circuit map formation.

**Development of the Cerebellum**

Soon after the cerebellar primordium is formed at the midbrain/hindbrain boundary, two primary germinal zones, the ventricular zone and the rhombic lip, sequentially generate various inhibitory and excitatory neurons, respectively. While the migration of cerebellar neurons extends well into postnatal development, work in rodents demonstrates that embryonic Purkinje cells settle into molecularly distinct parasagittal ‘clusters’, which appear to serve as a template around which circuit architecture is built. The mature circuitry of the cerebellum is organized into functional longitudinal zones. In addition to their unique circuit connectivity, Purkinje cell zones are marked by parasagittal stripes of gene and protein expression, the adult correlates of embryonic clusters. Parasagittal molecular domains are maintained even when the cerebellar surface exhibits very rapid and extensive growth along its anteroposterior axis during the stereotyped folding process called foliation. Afferent fibers arrive in the cerebellum during late embryonic and early postnatal development and terminate within specific folds in a crude map that reflects a positional code defined by Purkinje cell lineages and gene expression. Then, activity dependent mechanisms fine-tune afferent termination domains by allowing individual connections to be integrated seamlessly into longitudinal zones that can be identified by specific Purkinje cell stripes and are innervated by distinct subsets of afferent projections. The proper functioning of the cerebellum therefore requires an elaborate interplay between genetic- and activity-dependent mechanisms to guide its morphogenesis and establish its circuit connections.

Cerebellar Development from the Study of Human Cerebellar Malformation

The study of human cerebellar malformations is beginning to provide new insights regarding the basic developmental principles of the cerebellum. Currently, human patient populations with congenital developmental disorders are largely underutilized in basic research but they have proven to be valuable for identifying novel, significant developmental genes. Disruption of human cerebellar development is often severely handicapping but not lethal, making it amenable to genetic analysis. The structure of the human cerebellum facilitates the easy identification of malformations as its morphology, foliation, and lamination are stereotypical across individuals and its morphogenesis is well understood. In conjunction with advances in imaging techniques, this allows patients to be diagnosed with malformations at early post-natal or even fetal stages. While patient populations provide a great resource for researchers, they are not often employed due to several difficulties, including a lack of routine brain imaging on patients with developmental abnormalities, genetic heterogeneity among cerebellar patients resulting in the requirement of large sample sizes, and difficulties recruiting patients. Despite these obstacles, human cerebellar malformations have been used to identify cerebellar developmental genes. Gratifyingly, mutations in human RELN cause cerebellar hypoplasia, similar to the phenotype seen in the reeler mouse, demonstrating the validity of cross species comparisons. Once genes have been identified in human cerebellar malformation syndromes, mouse models have proven essential for deciphering the underlying developmental disruptions.

**Genetic basics of known cerebellar Disorders**

* **Joubert syndrome (JS)** which 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. JS is genetically heterogeneous and so far three genetic loci have been mapped to 9q34.3 (JBTS1: OMIM 213300), 11p12–q13.3 (JBTS2: OMIM 608091) and 6q23 (JBTS3: 608629). JBTS1 appears to represent the classic Joubert phenotype of pure cerebellar and midbrain–hindbrain junction involvement, although the JBTS3 gene is also associated with cerebral cortical abnormalities, most notably polymicrogyria. JBTS2, in addition to classical JS features, is associated with a variety of other organ systems, involving kidney, eye and liver. Mutations of AHI1 have recently been shown to cause a form of JS, but the function of this gene is currently unknown.
* **Nephronophthisis (NPHP)** is a kidney disorder that represents the most common heritable cause of end-stage renal disease in children and is characterized by tubular atrophy, interstitial fibrosis and development of renal cysts. There are five genes (nephrocystin 1–5) known to cause several forms of NPHP. Juvenile NPHP is most often caused by mutations in NPHP1, encoding nephrocystin. The most common mutation is a homozygous deletion that spans three contiguous genes. Conversely, cerebellar malformations have been identified in patients diagnosed with NPHP.
* **Bardet–Biedl syndrome** (BBS: OMIM 209900) is characterized by obesity, mental retardation, polydactyly, gonadal malformation, retinal dystrophy and renal dysfunction. Neurological malformations are unusual, but cerebellar abnormalities have been reported. Eight genes, BBS1–BBS8, have been identified to date and all of the encoded proteins have been localized to cilia and or implicated in ciliary function and assembly, including cytoskeletal reorganization and cytokinesis. In particular, BBS4 has been associated with components of IFT, a microtubule-dependent mechanism by which components are trafficked during assembly and maintenance of cilia and flagella
* **Ataxia- Telangiectasia:** This is a rare inherited disorder that affects the nervous, immune, 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), slurred speech and trouble moving their eyes to look side-to-side (oculomotor apraxia). Small clusters of enlarged blood vessels called telangiectases, which occur in the eyes and on the surface of the skin, are also characteristic of this condition.

Cause- Caused by mutations in the ATM gene. 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. 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 cerebellum are particularly affected by loss of the ATM protein. 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 tumors.

Inheritance Pattern- It is inherited in an autosomal recessive pattern, which means both copies of the ATM gene in each cell have mutations. Most often, the parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but do not show signs and symptoms of the condition. These individuals are called carriers.

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