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**Review on the developmental genetics of the cerebellum**

The cerebellum arises from both the mesencephalic and rhombencephalic vesicles of the neural tube and develops over a relatively long period of time between early embryogenesis and late childhood. Development of the cerebellum can be described in four basic stages.

In the first stage, characterization of cerebellar territory occurs at the midbrain–hindbrain boundary. Transplantation studies in chicken and mouse have found that the isthmus organizer (IsO), a region corresponding to the midbrain–hindbrain boundary expression, is crucial for specifying midbrain and cerebellar structures. At the isthmus, restricted expression of secreted factors, such as fibroblast growth factor 8, *FGF8* and *Wnt1*, the mammalian homolog of *Drosophila* wingless gene, as well as homeobox proteins *En1* and *En2* and paired box genes *Pax2* and *Pax5* are required for early specification of midbrain and hindbrain structures. In the second stage, two compartments for cell proliferation are formed. Purkinje cells and cells of the deep cerebellar nuclei are generated in the roof of the fourth ventricle, and granule cell precursors, as well as cells of the pre-cerebellar nuclei are formed in the rhombic lip. Development of Purkinje cells is not well understood, but they are known to secrete Sonic hedgehog which regulates proliferation of granule cells. By this time point, granule neuron precursors express a number of markers, *Math1, nestin, zipro1/RU49* and *Zic* genes 1, 2. Purkinje cells migrate radially to their final positions, whereas granule neurons migrate over the surface of the developing cerebellum, forming the external granule layer (EGL). In the third stage, cells of the EGL migrate inward along the processes of Bergman glia to their final position in the internal granular layer (IGL). Finally, cerebellar circuitry is established and further differentiation occurs. The lower portion of the rhombic lip also gives rise to cells of the pre-cerebellar nuclei such as the inferior olivary nuclei, which migrate to positions in the brainstem.

**Genetic bases of known cerebellar disorders.**

**Hereditary Ataxias**

Hereditary Ataxias are genetic, which means they are caused by a defect in a certain gene that is present from the start of a person’s life, inherited from your parents. Hereditary Ataxias can be divided into those that are dominantly inherited, passing from generation to generation due to a single copy of a defective gene passing from parent to child, and those that are recessively inherited, Ataxia seen in a single generation and is due to two copies of a defective gene; one passed from each parent (who are carriers) to the child. It is caused by a defect in a certain gene that makes abnormal proteins. The abnormal proteins hamper the function of nerve cells, primarily in your cerebellum and spinal cord, and cause them to degenerate.  The hereditary ataxias are a group of genetic disorders characterized by slowly progressive incoordination of gait and often associated with poor coordination of hands, speech, and eye movements. Frequently, atrophy of the cerebellum occurs.

**Autosomal Dominant Ataxias:** They include;

**Spinocerebellar Ataxia**

Spinocerebellar Ataxia is one specific type of Ataxia among a group of inherited diseases of the central nervous system. Genetic defects lead to impairment of specific nerve fibers carrying messages to and from the brain resulting in degeneration of the cerebellum (the motor coordination center of the brain). With the advancement of research more than 40 different genes of SCA have been found with SCA 1 being the first to be found.

**Episodic Ataxia**

Episodic Ataxia is clinically characterized by attacks of Ataxia with a clear onset of resolution. There are now eight recognized episodic Ataxia syndromes, numbered 1-8, in addition to late onset episodic Ataxia. The genes are known for EA1, EA2, ES5, and EA6. The best characterized are EA1 and EA2, the others are exceptionally rare and largely defined by single families.

**Autosomal Recessive Ataxias:** They include;

**Joubert syndrome**

It is disorder of brain development that may affect many parts of the body. It is characterized by the absence or underdevelopment of the cerebellar vermis (a part of the brain that controls balance and coordination) and a malformed brain stem (connection between the brain and spinal cord). Joubert syndrome and related disorders may be caused by changes (mutations) in any of many genes (some of which are unknown). The proteins made from these genes are either known or thought to affect cell structures called cilia. Cilia are projections on the cell surface that play a role in signaling. may be caused by mutations in any of many genes. Inheritance is usually autosomal recessive, but rarely it may be X-linked recessive.

**Friedreich’s Ataxia**

It is caused by an abnormality of a single gene called the Frataxin (FXN) gene. The abnormality can be passed from generation to generation by family members who carry it. Two copies of each gene are inherited; one copy from the mother and one copy from the father. An individual who has one copy of an altered or nonfunctioning FXN gene does not develop any neurological symptoms and is called a carrier.

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