17/MHS01/301

Neuroanatomy assignment

The proximate basis of primate brain expansion and the evolution of increased cognitive performance lies in changes in gene function and regulation. Identifying the genetic basis of phenotypic change can provide insights into how developmental mechanisms evolve, how they are constrained, and how changes at a cellular level contribute to broad-scale anatomical evolution . The potential to dissect the biological basis of brain and behavioural evolution motivates many genomic comparisons across primates . These have identified numerous genes associated with brain development with high rates of evolution

The cerebellum is an intriguing component of the central nervous system. From one perspective it is a famously simple neuronanatomical circuit constructed from a relatively few neuronal types and comprising a single uniform microarchitecture . Despite the conserved nature of its core functional neuronal partnership, formed between granule cell axons and Purkinje cell dendrites, it is also clear that the cerebellum is employed as a neural “comparator” in different ways in different species . From a predominantly proprioceptive and sensory role in fish, it has adopted more overt motor functions in mammal. In primates, including humans, a large proportion of the cerebellar cortex is in addition given over to interactions with regions of the cortex involved in cognition and judgment .

At embryonic day 8.5 (E8.5), the interaction between homeobox genes Otx2 and Gbx2 defines the Isthmic Organizer region , which orchestrates the development of cerebellar structures via the morphogenic activity of two secreted factors, Fgf8 and Wnt1 . After territorial specification, cerebellar histogenesis starts at E9 in the mouse. At this age the cerebellar anlage is comprised of two separate and symmetric bulges that, during the following days, grow and fuse together, giving rise to the unitary cerebellar plate comprising the vermis and two hemispheres . This developmental process is also characterized by the formation of two germinative compartments just above the opening of the fourth ventricle: the rhombic lip (RL), located at the outer aspect of the cerebellar plate, adjacent to the roof plate and the ventricular zone (VZ), facing the lumen of the fourth ventricle. These germinative districts are defi ned by the region-specifi c expression of two basic helix-loop-helix transcription factors: the pancreas transcription factor 1-a (PTF1A), expressed in the V, and the mouse homolog of Drosophila atonal (ATOH1), present in the RL . This spatially-restricted expression pattern defi nes the neurochemical compartmentalization of cerebellar precursors, as all GABAergic neurons (Purkinje cells, PCs, nucleo-olivary projection neurons of deep cerebellar nuclei, DCN, and all inhibitory interneurons - basket, stellate, Golgi and Lugaro cells-) originate from Ptf1a + precursor, while glutamatergic lineages (large projection neurons of DCN, unipolar brush cells, UBCs, and granule cells) derive from Atoh1 + progenitors . The two primary germinative epithelia disappear at birth. Dividing VZ precursors migrate into the cerebellar prospective white matter (PWM), whereas those of the RL move tangentially along the pial cerebellar surface, where they form the external granular layer (EGL). Postnatal neurogenesis is active in the secondary PWM and EGL epithelia up to the third postnatal week, in order to generate appropriate numbers of GABAergic and glutamatergic interneurons, respectively. The temporal schedule of generation of cerebellar phenotypes is also finely organized. Birthdating studies have shown that projection neurons are produced first, at the onset of cerebellar neurogenesis, while both inhibitory and excitatory interneurons are generated later, during late embryonic and early postnatal life

Cerebellar malformations are now widely diagnosed during pregnancy and associated with significant morbidity and mortality in the newborn period and throughout life. Given the broad range in prognosis and associated medical concerns, a working knowledge of these disorders and their causes is essential for obstetricians, perinatologists and neonatologists. For clinicians, it is most relevant to organize cerebellar malformations by their clinical and imaging features, which then directs additional diagnostic testing, medical monitoring for associated complications, and counseling about prognosis, treatment and recurrence risk. Distinguishing genetic disorders from similar conditions caused by extrinsic factors, such as infection, stroke, or prematurity, is particularly important to provide quality patient care. Cerebellar malformations may be classified as predominantly involving the cerebellum or involving both the cerebellum and brainstem. They may occur in isolation or as part of broader syndromes involving multiple systems. Though the cerebellum has long been recognized for its role in motor co-ordination, it also shapes the functions of other brain regions, especially cognition and affect, by processing external sensory and internally generated information to influence neocortical circuit refinement.

Cerebellar disorders and known genetics basis

1. Ataxia is defined as “an inability to coordinate voluntary muscular movements.” Ataxia describes a neurologic symptom that can be seen in a myriad of diseases and conditions. Ataxia can be progressive or static, and can present at any age. Identifying the etiology of ataxia can be a complex task. For example, ataxia may be caused by a lack of proprioception and processing of environmental information by the extremities, which makes ambulation difficult as the feet do not know where they are in space. This phenomenon is called a sensory ataxia, as can be seen in patients with peripheral neuropathies. Alternatively, vestibular dysfunction can also cause ataxia, such as patients with Benign Paroxysmal Positional Vertigo (BPPV). Ataxia may be caused by dysfunction of the cerebellum, the part of the brain that coordinates movements of muscles and maintains the body’s equilibrium. Common etiologies of cerebellar dysfunction include acquired forms (which can be related to nutritional, immunologic, or degenerative causes) and inherited causes (related to genetics). Differentiating acquired from inherited forms of ataxia can help determine the expected disease course, the etiology of the condition, treatment options that may be available, and assist in genetic counseling. Inherited etiologies involve a genetic or biochemical defect which leads to the formation of ataxia. A positive family history of similar conditions, physical exam findings, neuroimaging, and genetic testing can help make the diagnosis of an inherited ataxia.
2. X-linked infantile nystagmus is a condition characterized by abnormal eye movements. Nystagmus is a term that refers to involuntary side-to-side movements of the eyes. In people with this condition, nystagmus is present at birth or develops within the first six months of life. The abnormal eye movements may worsen when an affected person is feeling anxious or tries to stare directly at an object. The severity of nystagmus varies, even among affected individuals within the same family. Sometimes, affected individuals will turn or tilt their head to compensate for the irregular eye movement.

A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes in each cell. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two copies of the X chromosome), one altered copy of the gene in each cell can cause the condition, although affected females may experience less severe symptoms than affected males. Approximately half of the females with only one altered copy of the FRMD7 gene in each cell have no symptoms of this condition.

References:

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