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ASSIGNMENT TITLE: CEREBELLUM AND ITS CONNECTIONS

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

ANSWER: The cerebellum resides at the anterior end of the hindbrain and is classically defined by its role in sensory-motor processing. It contains over half of the mature neurons in the brain. The mature cerebellum has a simple cytoarchitecture yet the connections between its neurons are wired into a complex array of gene expressions and functional circuits. Two primary germinal zones generate the cells that make up the cerebellum. Each zone expresses a specific set of genes that establish the cell lineages within the cerebellar anlage. The various genes that control cerebellar development have been grouped into four and they include genetic with gene and genes for morphogenesis, physiology and metabolism. At cellular level, the cerebellum is composed of very few neuronal types each with distinct lamina and connected in stereotypical circuits.

Using insights gained from studies of sharks, paddlefish, chicks, mice and some other specimen, we focus on the three distinct aspects of cerebellar development that represent autonomous phases of growth which are the allocation of the cerebellar anlage, the significance of transit amplification and the generation of neuronal diversity. The current understanding of genetic basis of cerebellar development is derived primarily from the study of spontaneous and targeted mouse mutants. The territory that will generate the cerebellum –its anlage- is allocated during the early embryonic segmental phase of hindbrain development close to the boundary between the hindbrain and midbrain. Regulation of patterning in early phase is particularly important for the development of the uniquely mammalian midline expanded region of the cerebellum called vermis. For glutamatergic cells of cerebellum, this is a remarkably prolonged process that takes place at the most dorsal interface between neurons. Development of non-neural roof-plate tissue: the rhombic lip (in mouse, at E10.5). This phase generates the basic dichotomy between GABAnergic and glutamatergic cell types

that underlies the conserved Purkinje-granule cell circuit and it is also responsible for the diversity of cerebellum output connectivity across species. Cell type allocation precedes a third, distinct temporal phase of development that extends into early prenatal life (postnatal day 21 in mouse and up to 2 years in human). Final form of mammalian cerebellum is so much a product of the first and third phases of development. Cerebellar anlage sits between Hox and Otx domains. The anlage of the cerebellum is a product of mechanisms of segmentation that establish iterated rhombomeric subdivisions within its early hindbrain just after neural tube closure. Cerebellum arises from anterior hindbrain following the induction by the isthmic organiser of the fate-determining gene expression domains that prefigures this structure. Two critical determinants of regional identity are the orthodenticle homeobox 2 (Otx2) and gastrulation brain homeobox 2(Gbx2) and they are expressed in presumptive midbrain and hindbrain respectively and act coordinately with fibroblast growth factor 8 (Fgf8) to prevent mixing of cells across mid-hindbrain boundary. Immediately anterior to Fgf8, the wingless-type MMTV integration site family member 1 (Wnt1) is expressed and this member 1 is essential for midbrain and cerebellum development through its activation of Fgf8. The roof plate of rhombomere 1 largely gives rise to the choroid plexus and produces bone morphogenetic protein (BMP) and WNT signals that pattern the dorsal neural tube. Patterning and morphogenesis of the cerebellar anlage involves a hierarchy of signaling centres whose origins can be traced to the isthmic organizer. Normal cerebellar growth and morphogenesis depends on the integrity of the primary cilium that functions as a cellular antenna. Primary cilium acts as signaling hub, best known for its role in transducing signaling by the diffusible morphogen sonic hedgehog (SHH). Fgf17 and Fgf8 are a requirement for the growth of the vermis. Gbx2, Otx2 and the chromatin modifier chromodomain helicase DNA binding protein 7 (CHD7) have been found to link midbrain-hindbrain boundary specification with downstream Fgf signaling. Otx2 is at rostral boundary. Hox2 is at caudal boundary and Gbx2 is expressed in r1 abutting Otx2 and genes expressed at MHB. Foxc1 controls normal cerebellar development by regulating secreted growth factor signals.

GENETIC BASES OF KNOWN CEREBELLAR DISORDERS

The cerebellar disorders are the following: Cerebellar vermis hypoplasia (CVH), Dandy-walker syndrome (DWM), Joubert syndrome and related disorders (JSRD) and pontocerebellar hypoplasia (PCH).

CEREBELAR VERMIS HYPOPLASIA: Mutations in human RELN gene cause cerebellar hypoplasia. It is characterized by a small hypoplastic cerebellum with the vermis more affected than the hemispheres. Several CVH loci have known recessive or X-linked

inheritance.

DANDY WALKER MALFORMATION: Mutations in FOXC1, a transcription factor gene located in 6p25.3 locus causes DWM. Mendelian inheritance is rare. The genetics is most likely oligogenic.

JOUBERT SYNDROME AND OTHER RELATED DISORDERS: Mutations in different genes may lead to this syndrome. The genes include AHI1, ARL13B, CC2D2A, CEP290, INPP5E, NPHP1, RPGRIP1L and TMEM67. The main gene causing the syndrome is INPP5E which codes for inositol polyphosphate-5-phosphatase E. The disorder is autosomal recessive which are rare and with a population incidence of about 1 in 100,000.

PONTOCEREBELLAR HYPOPLASIA: Mutations in TSEN54, TSEN34 and TSEN2.

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