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**Write a concise review on the developmental genetics of the development of the cerebellum and known cerebellar disorders**

The cerebellum, a structure derived from the dorsal part of the most anterior hindbrain, is important for integrating sensory perception and motor control. While the structure and development of the cerebellum have been analyzed most extensively in mammals, recent studies have shown that the anatomy and development of the cerebellum is conserved between mammals and bony fish (teleost) species, including zebrafish. In the mammalian and teleost cerebellum, Purkinje and granule cells serve, respectively, as the major GABAergic and glutamatergic neurons. Purkinje cells originate in the ventricular zone (VZ), and receive inputs from climbing fibers. Granule cells originate in the upper rhombic lip (URL) and receive inputs from mossy fibers. Thus, the teleost cerebellum shares many features with the cerebellum of other vertebrates, and is a good model system for studying cerebellar function and development. The cerebellum functions in the control of smooth and skillful movements, and it is involved in higher cognitive and emotional functions (Rodriguez et al.,2005; Ito, 2008).

In zebrafish, as in mammals, the cerebellum contains several different types of neurons, which are categorized according to their function as excitatory or inhibitory neurons (Butler and Hodos, 1996; Altman and Bayer, 1997; Bae et al., 2009) The excitatory neurons use glutamate as their major neurotransmitter (glutamatergic neurons). They include granule cells, unipolar brush cells, and eurydendroid cells (the eurydendroid cells are probably equivalent to the deep cerebellar neurons in mammals), (Butler and Hodos, 1996; Meek et al., 2008). The inhibitory neurons utilize c-aminobutyric acid (GABA) and/or glycine (called GABAergic neurons hereafter), and include Purkinje cells and interneurons such as the Golgi and stellate cells. Basket cells, which are GABAergic interneurons that project their axons to the Purkinje cell somata, are present in the mammalian cerebellum, but have not been reported in the teleost cerebellum (Butler and Hodos, 1996). there are two major afferent fibers, the climbing and mossy fibers

The cerebellum is derived from the dorsal part of the anterior hindbrain. The formation of the cerebellar region is dependent on anteroposterior neural patterning that takes place during the late gastrula period. This establishes the isthmic organizer, which lies at the junction of the midbrain and hindbrain and necessary for the formation of the cerebellum and it contains 2 homeo domain containing transcription factors Otx2 & Gbx2 which plays important role in isthmus positioning, during late gastrulation isthmus specific expression of pax5, pax8 & fgF17 is activated.

- Development of granule cells: descendant of posterolateral URL progenitors remain in place and migrate to form granule cells at Eminentia granularis (eg)/ Locus caudalis cerebelli (LCa) the granule cells in external granule layer proliferate in response to sonic hedgehog (Shh) which is produced by purkinje cells at ohlb & atohlc are expressed in medial and caudal part of cerebellum by proliferating cells, neuronal progenitors in caudal domain gives rise to granule cells in LCa & EG , this development is controlled by genetic programs e.g atohl gene

- Development of purkinje cells : The ptfla+ expression and start to migrate dorsally, they end their migration at floral position corresponding to purkinje cell layer when they differentiate into purkinje cell, it is unclear whether only purkinje cells are derived from ptfla+VZ progenitors, the atohla+ & ptfla+ lineages are adjacent to each other and so migration of 2 lineages in opposite directions leads to formation of cerebellar layers, Shh produced by purkinje cells leads yup expansion of granule cells. The interaction between the two lineages may be important for proliferation and/or migration of granule cells and GABAnergic neurons

- Eurydendriod cells: Transmit information from purkinje cells extra cerebellar domains , there are two types of eurydendroid cells; olig2-expressing eurydendroid cells and calretinin immunoreactive (Cr-ir+) eurydendroid cells. Olig2 is derived from ptfla+VZ progenitor & atohla+ URL progenitors while that of Cr-ir+ is unknown, future studies are required in this area

Development of Neural circuits

- Efferent fibers: In addition to axons of eurydendroid cells, purkinje cells also send their axons outside the cerebellum too vestibular regions

- Afferent fibers : Inferior olive nuclei (IO) extend from climbing fibers which originate from ptfla+ progenitors in dorsal hind brain and terminates in dendrites of purkinje cells, there is little information about the mossy fibers that project from cerebellar glomeruli to granule cells & Golgi cells

- Parallel fibers & purkinje cell dendrites : purkinje cells extend their dendrites in the CCe at the same time the neural circuits have formed in molecular layer

- Cerebellum like structures : they contain granule cells, unipolar brush cells, stellate cells & principal cells they include medial octavolateral nucleus(MON) & marginal layer of optic tectum. In MON the crest cells function as principal cells and extend their dendrites to the cerebellar cortex where they receive Parallel fiber inputs from eminentia granularis (EG) I’m the cerebellum, they also receive afferent input from lateral line afferents.

In optic tectum pyriform cells act as principal cells and extend their dendrites superficially into marginal layer to receive parallel fibers from torus longitudinal (TL)

Pyriform cells (type 1 neuron) and outline cells express parvalbumin 7, glutamate receptor delta 2 (grid2) & retinoid related option receptor alpha 2 (rora2) whole granule cells express vglut1.

These data support the idea that neural circuits have functional similarity and they are generated by common or similar genetic program

A. The development, evaluation, and validation of new clinical scales for the assessment of disease severity and progression in cerebellar disease have gained increasing impact during the last years. There are various types of degenerative ataxias that share the common feature of cerebellar dysfunction but differ in the underlying neuro-degenerative pattern. Friedreich ataxia (FA), e.g., is primarily affecting dorsal root ganglia and spinal tracts while spinocerebellar ataxias mainly involve the cerebellum and brainstem. In addition, the clinical phenotype and the age of onset may vary considerably even in the same disease: listed below are some types of ataxia;

1. Autosomal recessive cerebellar ataxia (ARCA) : ARCAs are rare and encompass a group of genetic heterogeneous diseases with more than 20 different clinical types ;

| Type of ARCA | Mutated gene |
| --- | --- |
| Friedreich’s ataxia (FRDA) - | FXN |
| Ataxia telangiectasia (AT) | ATM |
| Ataxia with occulomotor apraxia type 1 (AOA1) | APTX |
| Ataxia with occulomotor apraxia type 2 (AOA2) | SETX |
| Ataxia with isolated vitamin E deficiency (AVED) | TTPA |
| Abetalipoproteinemia (ABL) | MTP |
| Cerebrotendinous xanthomathosis (CTX) | CYP27A1 |
| Spinocerebellar Ataxia  type 1 with axonal  neuropathy (SCAN1) | TDP1 |
| Marinesco-Sj€ogren  Syndrome (MSS | SILI |
| Cerebellar ataxia with CoQ deficiency | COQ2,PDSS1,PDSS2, CABC1, COQ9 |

According to the type of mutation, only FRDA is caused by a dynamic expansion and the remaining ARCAs are due to conventional mutations

2. Autosomal dominant cerebellar ataxia (ADCA) : A large number of more than 30 SCA (spinocerebellar ataxia) loci have been associated with ADCA phenotypes. The phenotypic classification by Harding (Harding 1982) that categorized three groups of ADCAs may be useful to perform an accurate genetic testing.

\* ADCA type I refers to ataxia plus impairment of other neurological systems the first genes to be tested are SCA1, SCA2, and SCA3.

\* ADCA type II is ataxia plus retinal degeneration, it is is almost exclusively associated with SCA7 mutations.

\* ADCA type III is described as pure cerebellar ataxia and a non-life-limiting disease, SCA6 and SCA12 should be the first genes to be analyzed.

As in other autosomal dominant disorders, each child of

an individual who suffer from an ADCA has a 50% chance of inheriting the mutation.

3. Episodic ataxia: Episodic ataxias (EAs) are autosomal dominant disorders characterized by intermittent episodes of ataxias. Seven loci have been associated with episodic ataxias and mutations in four genes have been reported. The most frequent types, EA-1 and EA-2, can be distinguished on clinical grounds. EA-1 manifests without vertigo and is associated with interictal myokymia, and EA-2 manifests with vertigo and is associated with interictal nystagmus . Both types of EA are due to mutations in ion channels. EA1 is caused by mutations in the KCNA1 gene that encodes an a-subunit of a voltage-dependent potassium ion channel, whereas EA-2 is caused by point mutations in the CACNA1A gene, which is translated in the a1A-subunit of the calcium-voltage dependent channel.

4. X-linked cerebellar ataxia : Some X-linked SCAs have been described (SCAX1 to SCAX5), but the involved genes remain uncharacterized in all of them. All these X-linked forms are congenital ones, except the SCAX4 type. Other congenital X-linked ataxias are syndromic forms associated with mental retardation, such as the X-linked syndromic mental retardation Christianson type (MRXS-Christianson).

5. Mitochondrial Cerebellar Ataxia :

Mitochondrial disorders refer to a group of diseases associated with abnormalities

of the mitochondrial energy metabolism, mainly the oxidative phosphorylation

(OXPHOS) (Zeviani 2001), which can result from defects of mitochondrial proteins, either coded by the mitochondrial (mtDNA) or by the nuclear DNA. This section refers to ataxias caused by mutations on the mtDNA and, therefore, inherited through the maternal line Some of the examples of mitochondrial disorders manifesting with ataxia include MELAS syndrome (mitochondrial myopathy, encephalopathy, lactacidosis, stroke

syndrome), MERRF (myoclonic epilepsy with ragged red fibers), NARP (neurogenic

muscle weakness, ataxia, and retinitis pigmentosa), and KSS (Kearns-Sayre syndrome)

Thus, nearly the 80% of individuals who suffer from MELAS carry the m.3243A>G mutation in the MT-TL1 gene encoding leucine transfer RNA gene (tRNA-Leu) (Yasukawa et al. 2000). Other mutations in the MT-TL1 gene or inother mtDNA genes, particularly MT-ND5, can also cause this disorder. The m.8993T>G in the MT-ATP6 (subunit 6 of mitochondrial ATP synthase) gene accounts for nearly 50% of cases with NARP (de Coo et al. 1996; White et al. 1999).

In the same sense, 80% of patients with MERFF are carriers of the m.8344A > G

mutation in the MT-TK gene which encodes for lysine transfer RNA gene (tRNA-Lys) (Shoffner and Wallace 1992). KSS can result in point mutations, although by far the majority of patients carry a large deletion of mtDNA (Moraes et al. 1989).

6. Idiopathic late-onset cerebellar ataxia(ILOCA): a term originally introduced by Harding (1981), comprise a variety of cerebellar syndromes whose underlying mechanisms are still unknown and that may present with a pure cerebellar syndrome or with additional non-cerebellar features. Clinically ILOCA syndromes are heterogeneous; course and prognosis vary markedly between patients. Therefore, to diagnose accurately ILOCA cases, genetic ataxias should be excluded in patients younger than 50 years. First it is advised to screen for ARCA, mainly the FXN gene and in males, for X-linked ataxias. Then, screening for SCA genes is also recommended. Many times, ILOCA patients are easily mistaken for SCAs because these patients can be interpreted as the resulting of de novo dominant mutations.

B. The cerebellum is one of the first brain structures to begin to differentiate, and its

cellular organization continues to change many months after birth. This prolonged

developmental process makes the cerebellum vulnerable to developmental disorders (Wang and Zoghbi 2001) listed below are some malformations which occur during cerebellum embryology;

1. Holoprosencephaly of the Hindbrain: Rhombencephalosynapsis (RMS) RMS was considered to be an abnormal development of the vermis with subsequent undivision of the cerebellar hemispheres .

It may be explained by an embryological defect in the dorsoventral patterning at

the isthmus, which only alar ventricular zones defects (Barkovich et al. 2009). It is

probably due to an underexpression of a dorsalizing organizer gene (Sarnat 2000). Associated intracranial anomalies include cortical malformations, aquaduct

stenosis, hydrocephalus, absence of the septum pellucidum, anomalies of the limbic system, and multiple cranial suture synostoses (Barkovich 2005). Extracranial

anomalies are very rare and may affect the musculoskeletal, urinary tract, cardiovascular and respiratory systems (Chemli et al. 2007).

2. Dystroglycanopathies with Cobblestone Malformations: Congenital Muscular Dystrophies;

(CMD) are clinically heterogeneous autosomal recessive disorders characterized by hypotonia, muscle weakness, and contractures

at birth or in the first few months of life (Barkovich 1998). Recent studies have

indicated that impaired O-mannosylation of alpha-dystroglycan is associated with

CMD. This new clinical entity is called dystroglycanopathy and includes Fukuyama congenital muscular dystrophy (FCMD), WalkerWarburg syndrome (WWS), muscle–eye–brain disease (MEB), and congenital muscular dystrophy without recognized brain malformations (Muntoni et al. 2002). Mutations in different genes (POMT1, POMT2, POMGNT1, FKRP, and LARGE) have been identified in patients with alpha-dystroglycanopathies (Clement et al. 2008).

3. Ciliary and Centrosomal Dysfunction: Joubert Syndrome and Related Disorders (JSRD)- they are complex midbrain– hindbrain malformations also known as the molar tooth malformations. The neuroradiological hallmark of JSRD is the molar tooth sign.The molar tooth sign is defined by a peculiar appearance resembling a molar tooth secondary to an abnormally deep interpeduncular fossa and enlarged superior cerebellar peduncles on axial images at the pontomesencephalic level. JSRD is characterized by lack of decussation of the superior cerebellar peduncles, central pontine tracts, and corticospinal tracts (Barkovich 2005), which suggests that it may be linked with defects of axon guidance (Louie and Gleeson 2005). JSRD seem to be caused by mutations of genes encoding ciliary and centrosomal proteins (Barkovich et al. 2009)

4. Mesenchymal-Neurepithelial Signaling Defect: Cerebellar and Posterior Fossa Malformations - Posterior fossa anomalies include DandyWalker malformation (DWM), cerebellar vermis hypoplasia (CVH), mega-cisterna magna (MCM) with cerebellum vermis hypoplasia, isolated mega-cisterna magna, and arachnoid cysts of posterior fossa (Aldinger et al. 2009). The FOXC1 gene is expressed in the posterior fossa mesenchyme overlying the cerebellum. Specific loss of FOXC1 and general defects in mesenchymal signaling may result in cerebellar and posterior fossa malformations, including CVH, MCM, and DWM (Aldinger et al. 2009).

5. Cerebellar Hypoplasia : Cerebellar hypoplasia is defined as a small or incompletely formed cerebellum with normal folia and fissures. Cerebellar hypoplasia can be the result of many different processes: dorsoventral patterning defects decreased proliferation and increased apoptosis due to abnormal and late migration of granule cells or cerebellar disruption (Barkovich et al. 2009). Developmental encephalopathies include mental retardation, autism spectrum disorders, schizophrenia, Rett syndrome, and other similar disorders.

6. Cerebellar Agenesis: is an extremely rare condition in which patients show minute cerebellar tissue, usually corresponding to remnants of the lower cerebellar peduncles, anterior vermal lobules, and flocculi. Patients with involvement of the phylogenetically most ancient structures (complete or partial cerebellar vermis agenesis) show themore severe clinical picture, in particular severe pervasive impairments in socialand communication skills (autism or autistic-like behavior), in behavior modulation (self-injury and aggressiveness), and markedly delay in language acquisition, especially in language comprehension. Pathogenesis of cerebellar development anomalies including partial or total. cerebellar agenesis is still under debate. They may be secondary to a large number of pathological events either genetic or acquired and genetic factors could contribute to susceptibility to disruption (Boltshauser 2008; Poretti et al. 2009). Genetic causes include chromosomal copy number aberrations such as trisomies 9, 13, and18, chromosomal rearrangements such as del 1q44, del 22q11.2, dup 9p, del 13q2, del 2q36.1, and del 3q24 (Melaragno et al. 1992; Chen et al. 2005; McCormack et al. 2003; Ballarati et al. 2007; Jalali et al. 2008; Boland et al. 2007; Hill et al. 2007; van Bon et al. 2008), and single-gene mutations such as OPHN1, FOXC1,CASK, and ZIC (Zanni et al. 2005; Aldinger et al. 2009; Grinberg and Millen 2005;Najm et al. 2008). Sometimes, cerebellar malformations are associated with more complex brain malformations genetically determined such as lissenchephaly (Ross et al. 2001; Miyata et al. 2004), bilateral frontoparietal plymicrogiria due to mutations of GPR56 gene (Chang et al. 2003), malformation of cortical development due to RELN gene (Hong et al. 2000), some types of congenital musculardystrophies (Barkovich 1998; Philphot et al. 2000), and pontocerebellar hypoplasia(Uhl et al. 1998; Barth 2000). Recently, a mutation in PTF1A gene (10p12.3 locus) was described (Sellick et al. 2004; Millen and Gleeson 2008; Tutak et al. 2009)

C. Dandy Walker Malformations : It is a congenital brain malformation that is characterized by agenesis of cerebellar vermis, cystic dilation of the fourth ventricle, and large posterior fossa with upward displacement of the tentorium, lateral sinuses, and torcular (Dandy and Blackfan 1914) . The exact etiology of DWM remains unknown; nevertheless, atresia of the foramina of Magendie and Luschka have been suggested as possible causative agents that result in blockage of cerebrospinal fluid flow (Alexiou et al. 2010a) Brain malformations that can be observed in DWM are usually porencephaly; gray matter heterotopias; absence or hypoplasia of the corpus callosum; interhemispheric cysts; malformations of cerebral gyri and folia; malformations of the dentate nucleus, the inferior olivary nucleus, and the brainstem; hamartoma of the tuber cinereum; crouzon syndrome; Klippel–Feil deformity; and spina bifida (Sawayaand McLaurin 1981; Osenbach and Menezes 1992; Kalidasan et al. 1995; Alexiou andProdromou 2010) it is also associated with several systemic abnormalities such as as ventricular septal defects, patent ductus arteriosus, transposition of the great arteries, congenital pulmonary stenosis, cardiomegaly, and pericardial effusions are usually reported. Urogenital anomalies usually are vesico-ureteral reflux, hydrocele, polycystic kidneys, and renal agenesis (Menon et al. 2006). Gastrointestinal anomalies that have been reported are mega rectum, mega sigmoid, and duodenal atresia. Facial anomalies are usually microphthalmia, strabismus, hypertelorism, facial angioma, cataract, retinal dysgenesis, cleft palate, and neurocutaneous melanosis, whereas skeletal anomalies are usually malformed limbs and finger or toe syndactyly and polydactyly (Kalayci et al. 2006; Marnet et al. 2009)

D. Autism spectrum disorders

Autism is a neurodevelopmental disorder that is characterized by deficits in communication, behavior, and cognition (APA 1994). There are both genetic (reviewed by Abrahams and Geschwind 2010; El-Fishawy and State 2010) and environmental(reviewed by Kinney et al. 2008; Herbert 2010) contributions to autism. The cerebellum has roles in multiple domains impaired by autism including emotional processing, executive function, working memory, motor control, and language. In the cerebella of subjects with autism, there is extensive pathology including vermal hypoplasia, changes in gray and white matter, changes in Purkinje cell density and area, and disrupted connections to the frontal cortices. Markers of GABAergic function (GAD65/67, GABAA, and GABAB receptors), proper brain development (Reelin), apoptosis (p53, PTEN, Bcl-2), inflammation and oxidative stress (GFAP, 3-nitrotyrosine) have been shown to display altered expression. Finally, CSAs provide further evidence of the cerebellum’s influence in multiple domains including both movement and cognition.

E. Progressive myoclonic epilepsies (PME):

are a group of rare disorders characterized by the occurrence of seizures, myoclonus, and progressive neurological dysfunction usually beginning in childhood and adolescence,

The commonest causes of PME and their genetic base will be discussed below ;

- Unverricht–Lundborg Disease (ULD, Baltic Myoclonus) : it is inherited as an autosomal recessive disorder with the genetic mutation (in CSTB gene, formerly called EPM1 gene) localized on chromosome 21q22.3. The main mutation is an unstable expansion of a dodecamer repeat in the 5’ untranslated promoter region, the disease can occasionally be caused also by several other mutations that affect one or two nucleotides in CSTB. ULD, widespread degenerative changes are found in the central nervous system (CNS) without inclusion bodies. The loss of Purkinje cells and granule cells in the cerebellum most likely explains the ataxia

- Myoclonic Epilepsy and Ragged Red Fibers (MERRF) : was first recognized by Fukuhara et al. (1980) when he described the classic signs and symptoms of this disorder: myoclonus, seizures, ataxia, and the presence of ragged red fibers in the muscle biopsy. The mutation in the mitochondrial DNA was found by Shoffner et al. (1990).

MERRF is maternally inherited. There is a highly specific, although not exclusive, point mutation at nt 8,344 in the tRNA Lys gene of mitochondrial DNA (Shoffner et al. 1990). Other mutations have been identified, including a tyrosine to cytosine substitution (8,356 T ! C) and a guanine to

adenosine (8,363 G ! A) in the same gene and a 15,967 G ! A tRNAPro mutation

(Shahwan et al. 2005; Blakely et al. 2009) In some patients the mutation is unknown

- Cherry-Red Spot Myoclonus Syndrome (Type 1 Sialidosis): Sialidosis is an autosomal recessive lysosomal storage disorder due to mutations of the lysosomal neuraminidase gene on chromosome 6p21 (Pshezhetsky et al. 1997).Neuraminidase removes terminal sialic acid residues from sialyl-oligosaccharidesreleased during glycoprotein degradation (Kashtan et al. 1989)

- Lafora disease : LD is an autosomal recessive disorder due to the mutation of the EPM2A gene located in chromosome 6Q24 in 65–85% of the affected families. Multiple mutations in EPM2A gene have been described, including missense, frameshift, insertion, and deletion mutations of different sizes (Chan et al. 2003). This gene codes for a 331-amino-acid protein, called laforin , it

contains also a carbohydrate-binding module with which it appears to bind glycogen (Chan et al. 2003) Another locus for LD named NHLRC1 (EPM2B) has been identified at 6p22 (Chan et al. 2003). The affected gene codes for malin, an E3 ubiquitin ligase which promotes the degradation of proteins, including laforin, involved in glycogen metabolism (Lesca et al. 2010)

- Gaucher disease : GD is caused by a deficiency of the enzyme glucocerebrosidase. Glucocerebrosidase deficit results from mutations of the glucocerebrosidase gene itself or, rarely, from mutations in the gene of saposin C, a glucocerebrosidase activator(Kleinschmidt et al. 1987). All forms of GD are inherited in an autosomal recessive mode. The glucocerebrosidase gene is located on chromosome 1, band q21(Barneveld et al. 1983). Over 300 mutations of this gene have been described (Grabowski 2008). Some genotype/phenotype correlations exist, but there are substantial exceptions.

- Dentatorubropallidoluysian Atrophy (DRPLA) : DRPLA is characterized by an autosomal dominant inheritance and is due to the expansion of an unstable trinucleotide (CAG) repeat in exon 5 of the B37 gene on chromosome 12p13.31 (Koide et al. 1994; Nagafuchi et al. 1994). The DRPLA gene encodes for an 1,184-amino-acid protein of unknown function, called atrophin-1 or drplap. Atrophin-1 is located in cytoplasm and nucleus of neurons (Schilling et al. 1999) and contains polyglutamine which have the ability to aggregate

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Handbook of the Cerebellum and Cerebellar Disorders Mario Manto • Donna L. Gruol

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