**Developmental Genetics of Cerebellum and Genetic Bases of Cerebellar Disorders**

**Introduction**

The cerebellum is situated in the posterior cranial fossa and is covered superiorly by the tentorium cerebelli. In adult, the weight of the cerebellum is about 150g. It is the largest part of the hindbrain and lies posterior to the fourth ventricle, the pons, and the medulla oblongata. The cerebellum is somewhat ovoid in shape and constricted in its median part. It consists of two cerebellar hemispheres joined by a narrow median vermis.

Cerebellum plays critical roles in learning sensorimotor tasks ([Manto, 2010](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B51)). For instance, it is widely accepted that the olivocerebellar tract in one of the key pathways contributing to learning of new motor skills ([Ito, 2006](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B39)). However, although the involvement of cerebellar circuits in motor learning is known to be critical, their precise role in the acquisition and storage of new motor abilities or rather in the performance of the acquired motor skills is still a matter of debate.

This review covers recent advances in the understanding of the gene networks contributing to cerebellar development.

## The Key-Features of Cerebellar Development

The major features of cerebellar development can be briefly summarized as follows. Neuronal populations are generated in a sequential manner. The inhibitory interneurons emerge from the ventricular zone and the glutamatergic neurons are generated by the rhombic lip ([Carletti and Rossi, 2008](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B13)). After generation of cerebellar nuclei, the external granular layer is formed from precursors of granule cells originating from the rhombic lip. Granule cells will migrate to form the internal granular layer. It is interesting to note that these events occur at the third trimester of development in human. Survival and maintenance of Purkine neurons and granule cells is dependent on the antiapoptotic protein Lifeguard, which is highly expressed in the cerebellum and is strongly upregulated during postnatal brain development ([Hurtado de Mendoza et al., 2011](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B37)). Lifeguard antagonizes the FAS pathway. FAS receptors tune neuronal survival following trophic factors deprivation ([Raoul et al., 2000](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B64)). Lifeguard affects cerebellar size, internal granular layer thickness, and Purkinje cell development, suggesting that lifeguard could participate in the pathogenesis of various human cerebellar disorders characterized by cerebellar atrophy. Glutamatergic unipolar brush cells migrate to the internal granular layer. Whereas the ventricular zone will lose its progenitors at late embryogenic stages, the rhombic lip remains active until postnatal period.

## Cerebellum, Hormones, and Neurosteroidogenesis

The relationship between circulating hormones and cerebellar development is well demonstrated. In particular, thyroid hormone plays a critical role in brain development ([Koibuchi, 2008](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B43)). The thyroid hormone receptor is a ligand-regulated transcription factor binding to a specific DNA sequence called thyroid-hormone-responsive element. The receptor recruits various coregulators such as coactivator and corepressor in a ligand-dependent manner to modulate the transcription of target genes ([Koibuchi, 2008](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B43)). It may also interact with other nuclear receptors such as Rora (retinoic-acid-related orphan receptor alpha; see below) whose expression is regulated by the thyroid hormone during the first postnatal two weeks.

In perinatal hypothyroidism, the growth and branching of Purkinje cell dendrites are greatly reduced, there is a reduction of synapses between granule cells and Purkinje neurons, migration of granule cells to the internal granule cell layer is delayed and synaptic connectivity within the cerebellar cortex is deficient ([Nicholson and Altman, 1972](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B56), [Koibuchi et al., 2003](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B44), [2008](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B43)).

**Genes and cerebellar growth**

The Engrailed-2 Gene

The engrailed (En) homeobox transcription factor family is critical for the patterning of cerebellar lobules and for Purkinje cells protein stripes ([Kuemerle et al., 1997](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B45)). The En1/2 regulates the targeting of mossy fiber systems to subsets of cerebellar lobules, showing a main role for the afferent topography in the cerebellar circuitry ([Sillitoe et al., 2010](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B72)). Initially, the En1/2 mRNA/protein are expressed in the ventricular zone. During early post-natal cerebellogenesis, En1/2 are expressed in spatially restricted patterns in most cell types. It is plausible that En1/2 are implicated in neurodevelopmental disorders such as autism spectrum disorder (see also below). Indeed, mutant mice EN2−/− show neurobehavioral and neurochemical deficits suggestive of autism spectrum disorder ([Cheh et al., 2006](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B16)).

Math1

The specification and differentiation of glutamatergic lineages is dependent upon Math1, a transcription factor of the bHLH class. Math1 is critical for the proper development of the granular layer of the cerebellum. Mice deficient in Math1 show a loss of glutamatergic neurons in cerebellar nuclei, a loss of external granular layer and unipolar brush cells. In addition, Math1 null embryos lack interneurons giving rise to the spinocerebellar and cuneocerebellar tracts ([Bermingham et al., 2001](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B8)).

Ptf1a and Ascl1

Cerebelless mutants have a deficit in the transcription factor Ptf1a (pancreatic transcription factor 1a). They show a lack of Purkinje cells and gabaergic interneurons. It has been demonstrated that climbing fiber neurons are derived from the Ptf1a domain ([Yamada et al., 2007](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B91)). In Ptf1a null mutants, immature climbing fiber neurons cannot migrate or differentiate, causing a failure in the formation of the inferior olivary nucleus. Ptf1a is also involved in the control of fate and survival of neurons during development. In human, mutations of Ptf1a are associated with cerebellar agenesis ([Sellick et al., 2004](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B71)).

Ascl1 directs ventricular neuroepithelium progenitors toward inhibitory interneuron fate and suppresses the astrocytic differentiation ([Grimaldi et al., 2009](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B31)). Mice lacking Ascl1 in the cerebellum exhibit a major decrease of cerebellar interneurons and an imbalance between oligodendrocytes and astrocytes ([Sudarov et al., 2011](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B76)).

Rora (Retinoic-Acid-Related Orphan Receptor Alpha) Gene

Rora is a transcription factor encoding a retinoid-like nuclear receptor which is highly expressed in the cerebellum ([Hamilton et al., 1996](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B33)). Rora belongs to the steroid-thyroid hormone receptor superfamily ([Koibuchi, 2008](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B43)). Its endogenous ligand is cholesterol which is abundantly present in each cell. Therefore, Rora acts as if it is a constitutively active nuclear receptor ([Koibuchi, 2008](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B43)). It was initially thought that Rora was exclusively expressed in neurons, but recent data show that it is also expressed in glial cells especially in astrocytes ([Journiac et al., 2009](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B42)). Rora plays a pivotal role in the development of the cerebellum, olfactory bulb, and retina ([Jetten, 2009](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B40)). However, its functions extend beyond development. For instance, Rora also protects neurons against oxidative stress and shows an anti-inflammatory action by inhibiting the NF-Kappa-B pathway ([Delerive et al., 2001](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B23); [Boukhtouche et al., 2006](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B11)).

The autosomal recessive staggerer mutation is associated with a severe degeneration of Purkinje neurons with a nearly total absence of granule cells at the end of the first postnatal month ([Landis and Sidman, 1978](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B46)). The homozygous mouse Rorasg/Rarasg is highly ataxic, whereas the heterozygous mouse Rora+/Rarasg appears phenotypically normal, showing disabilities during challenging tasks.

Reelin

The external granular layer promotes Purkinje cell migration by secreting reelin (RELN), an extracellular matrix component attracting or repealing precursors and axons during development, acting as an extracellular signaling molecule. Reelin deficient mice (Reeler) show a severe cerebellar hypoplasia. They exhibit Purkinje cell migration defects and cerebellar nuclei are impaired. Foliation is absent. Reelin continues exerting activities beyond birth. It modulates long-term potentiation and is thus involved in learning ([Beffert et al., 2004](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B7)). In the adult brain, Reelin regulates structural and functional properties of synapses. Its overexpression may increase markedly the long-term potentiation responses and it has been proposed that Reelin controls developmental processes remaining active in the adult brain ([Pujadas et al., 2010](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B63)). In human, reelin might be implicated in some forms of lissencephaly (due to neuronal migration defect) and could contribute to the pathogenesis of autism.

**Neurodevelopmental Disorders**

Thanks to novel perinatal neuroimaging techniques, cerebellar malformations are increasingly recognized in the fetal period ([Bolduc et al., 2011](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B10)).

* A typical example is Joubert syndrome. The disorder presents with developmental delay, hypotonia, impaired respiration, abnormal eye movements, and ataxia ([Joubert et al., 1969](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B41)). Motor learning is strongly impaired. The “Molar tooth sign” (deep interpeduncular fossa, enlarged superior cerebellar peduncles which are more horizontally oriented and hypoplastic cerebellar vermis) is very suggestive. **Joubert syndrome is associated with mutations of genes encoding components of the primary cilia.** Interestingly, primary cilia are determinant for sonic hedgehog signal transduction ([Vaillant and Monard, 2009](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B84)). Disruption of primary cilia formation blocks the proliferation of neural progenitors of granule cells mediated by sonic hedgehog ([Spassky et al., 2008](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B74)).
* Autism spectrum disorders are characterized by difficulties in communication, social skills, and repetitive behavior. Cerebellar networks might be critically involved in the pathogenesis of autism. An immune dysfunction with local inflammation contributes to the pathogenesis of autism ([Wei et al., 2011](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B87)). **The expression of IL-6 is increased in the cerebellum of autistic patients. IL-6 impacts upon the development of the cerebellum, impairing neural cell adhesion, migration, and causing an excessive formation of excitatory synapses (**[**Wei et al., 2011**](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B87)**).**
* Another disorder clearly associated with learning disabilities is rhombencephalosynapsis, a malformation of the hindbrain characterized by fusion of the cerebellar hemispheres and dentate nuclei. It is assumed that the disorder is due to a failure of dorsal patterning at the midbrain-hindbrain boundary ([Pasquier et al., 2009](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B61)). Other cerebellar malformations which are encountered in daily practice include Dandy–Walker malformation, vermis hypoplasia, mega cisterna magna, and posterior fossa retrocerebellar cyst. Sonic hedgehog might also be involved in the pathogenesis of Dandy–Walker malformation through a contribution of Zinc finger transcription factors which modulate the sonic hedgehog pathway ([Aruga, 2004](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B5)).
* Mutations of Herc Gene: Proteins with HECT domains act as ubiquitin ligases. Recently, it has been shown that **mutations in the highly conserved N-terminal RCC1-like domain of the HERC1 protein cause a progressive Purkinje cell loss leading to severe ataxia with reduced growth and lifespan** in homozygous mice aged over two months (tambaleante mutant mice; [Mashimo et al., 2009](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full#B53)). Activities of the proteins encoded by the HERC gene family are critical in a number of important cellular processes such as cell cycle, cell signaling, and membrane trafficking. It is now established that they play a key contribution in the physiology of Purkinje neurons.

**Conclusion**

In this mini-review, we have summarized recent advances in our understanding of the molecular mechanism governing cerebellar development. The identification of several pathways which are potential targets for novel therapies in the future, such as cerebellar neurosteroidogenesis, En1/2, Math1, Ptf1a, Rora, is now bringing hope in a field which has often remained neglected because of a lack of understanding of the molecular events leading to the malformations. There is still a growing need to identify new targets, since neurodevelopmental disorders are heterogeneous and will impact upon the whole life of patients in most cases. Protecting the developing cerebellum is now attracting the interest of the scientific community, especially with discoveries of the roles of the cerebellum in cognitive skills. Very preterm neonates are an example of a population of patients at risk and which could benefit from neuroprotecting actions.

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