NEUROANATOMY.

NAME: EMMAN-UGHEOKE ESIRO GENEVIEVE.

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

Developmental genetics of the cerebellum.

The Engrailed-2 gene is a major actor of the specification of cerebellar cell types and late embryogenic morphogenesis. Math1, expressed by the rhombic lip, is required for the genesis of glutamatergic neurons. Mutants deficient for the transcription factor Ptf1a display a lack of Purkinje cells and gabaergic interneurons. Rora gene contributes to the developmental signaling between granule cells and Purkinje neurons. The expression profile of sonic hedgehog in postnatal stages determines the final size/shape of the cerebellum. Many genes, including *En1*, *En2*, *Pax2*, *Wnt7b*, and some of the ephrins and their receptors, show characteristic patterns of spatial expression in the cerebellum, but only *En2* has been studied specifically for its role in compartmentalization. In addition to the patterning genes, several other gene families, such as the heat shock proteins and proteins involved in neuronal migration, are also expressed in specific patterns. Spatial- and temporal-specific knockout strategies should yield more information about the roles of these genes in patterning the cerebellum.

Genes affecting the development impact upon the physiological properties of the cerebellar circuits. For instance, receptors are developmentally regulated and their action interferes directly with developmental processes. Another field of research which is expanding relates to very preterm neonates.

* **Genetic bases for cerebellar disorders.**

## 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. 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. 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. Indeed, mutant mice EN2−/− show neurobehavioral and neurochemical deficits suggestive of autism spectrum disorder

**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.

**Ptf1a and Ascl1**

Cerebellar 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). 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" \l "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" \l "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 and Cerebellar Development**

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" \l "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

**The Chemokine Receptor 4 (CXCR4)-Chemokine Ligand 12 (CXCL12) System**

Chemokines and their receptors are determinant in cell migration and in organogenesis ([Zou et al., 1998](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B92)). CRXC4 and CXL12 mutant mice show proliferating granule cell progenitors located in deeper location ([Zou et al., 1998](https://www.frontiersin.org/articles/10.3389/fnana.2012.00001/full" \l "B92)). Down-regulation of CXCR4 causes an inward radial migration of granule cells precursors. The chemoattractant SDF-1α and its receptor CXCR4 attract the cerebellar granular neuronal precursors to the outer external granular layer and promote an increase of the sonic hedgehog mitogenic effect.