Chapter 11
Development and Diseases
Development of the nervous system is a complex process that involves multiple steps. Occasionally, errors in the normal program of development can lead to various diseases states.
Development of the Nervous System

Fertilization

Cleavage (Blastula, Gastrula)

Neuronal Induction-
Neuroblast Formation

Cell Migration

Axon Growth/Target innervation

Differentiation

Functional Nervous System

Reeler mutation
Congenital intestinal aganglionosis or Hirschprung disease

Spina Bifida

MASA syndrome
Optic nerve hypoplasia
Neurulation Disorders: Spina Bifida

Spina bifida consist of a broad range of malformations that is caused by a defect in primary neurulation and failure of the neural tube to fuse in the caudal regions.

Neurulation is the process by which the neural plate folds to form the neural tube in the early embryo.

From Estibeiro et al., 1993
Spina bifida may be caused by multiple factors including family history, inadequate intake of folic acid, anticonvulsant drugs acting as teratogens (valproid acid).
Spina Bifida

- Spina bifida may be caused by genetic mutations

- In mice, mutation of Pax3 give rise to the Splotch phenotype

- Pax3 control formation of neuroepithelial basal lamina. Disruption of this event will result in failure of the neural tube to fuse

From Estibeiro et al., 1993
Disorders of Migration

The development of the cerebellum occurs in four basic steps:

1) Characterization of cerebellar territory in the hindbrain
2) Formation of two proliferation zones that give rise to Purkinje neurons and granule cells
3) Inward migration of granule cells
4) Formation of cerebellar circuitry and further differentiation
The Reeler Mutation Disrupts Cerebellar Development and Causes Ataxia

Reelin is a large extracellular matrix molecule produced by Granule cells.

In the absence of reelin, Purkinje cell migration is disrupted.
Disorders of Migration

- Congenital intestinal ganglions (or Hirschprung disease) is characterized by the complete lack of ganglion cells in the enteric plexus.

- Hirschprung disease occurs when neural crest cells fail to migrate into the gastrointestinal tract. Disruption of normal migration occurs because a mutation of the ret proto-oncogene (loss of function mutation).
Disorders Involving Trophic Factors

- Hyperganglionosis is another disorder affecting the enteric plexus and is characterized by an increased number of ganglion cells in the plexus.

- Ganglioneuronomas is a particular type of hyperganglionosis that occurs due to a missense mutation in the Ret-proto-oncogene.

From Airaksinen & Saarma, 2002
Loss of netrin-1 in the optic disk results in RGC axons that fail to exit the retina.

This condition will result in optic nerve hypoplasia.

From Oster & Sretavan, 2005
Neural cell adhesion molecules of the immunoglobulin superfamily are important components of the network of guidance cues and receptors that govern axon growth and guidance during development. L1 is one member of CAM that are related by structure and sequence (L1, NgCAM, NrCAM)

From Kewnrick & Doherty, 1998
Each member of the L1 subfamily contains six immunoglobulin-like domains linked to five fibronectin type III domains on the extracellular surface, although variations on this theme are produced by alternative splicing of RNA for some proteins.

L1 and related molecules mediate cell–cell adhesion through Ca\(^{2+}\)-independent homophilic or heterophilic binding at the cell surface.

From Kewnrick & Doherty, 1998
Human Diseases Involving L1

MRI studies indicate that L1 mutations disrupt axon guidance and result in hypoplasia of long axonal tracts in the corpus callosum and the corticospinal tract.

From Kewnrick & Doherty, 1998
Developmental Disorders Caused by Drug Exposure

Exposure to drugs during early embryonic development can have long-lasting implications for brain structure and function. Effects on the developing nervous system, before homeostatic regulatory mechanisms are properly calibrated, differ from those on mature systems. Permanent alterations in brain function are induced by early drug exposure, producing hypo- or hyper-responsiveness to environmental or pharmacological challenges later in life.

From Bradley et al., 1997

Ethanol exposure induces significant cell lost in developing chick embryos.
Human Diseases Involving L1

Mutations in the human L1 gene are responsible for X-linked hydrocephalus, MASA syndrome and spastic paraplegia type 1. MASA syndrome is an extremely rare inherited disorder that is one of several disorders known as X-linked mental retardation (XLMR) syndromes. The acronym MASA stands for (M)ental retardation, (A)phasia, a diminished ability to communicate by speech, writing, and/or signs, (S)huffling manner of walking (gait), and (A)dducted thumbs, thumbs that are flexed inward toward the palm. Shuffling gait may be due to impaired control of voluntary movements and progressive rigidity of muscles in the legs (spastic paraplegia). Adduction of the thumbs may be due to absence or underdevelopment (hypoplasia) of certain muscles (extensor pollicis longus and/or brevis muscles) of the hand near the thumb.