Disorders of Neurodevelopment

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Course News

Final Exam

Thursday, Dec 20
1:30pm

In MoosT 2-620

Discussion

You first discussion reports are in the back of the room.
Please take yours.

Paper discussion next Friday!

Please come prepared or do not come!

Disorders of Nervous System Development

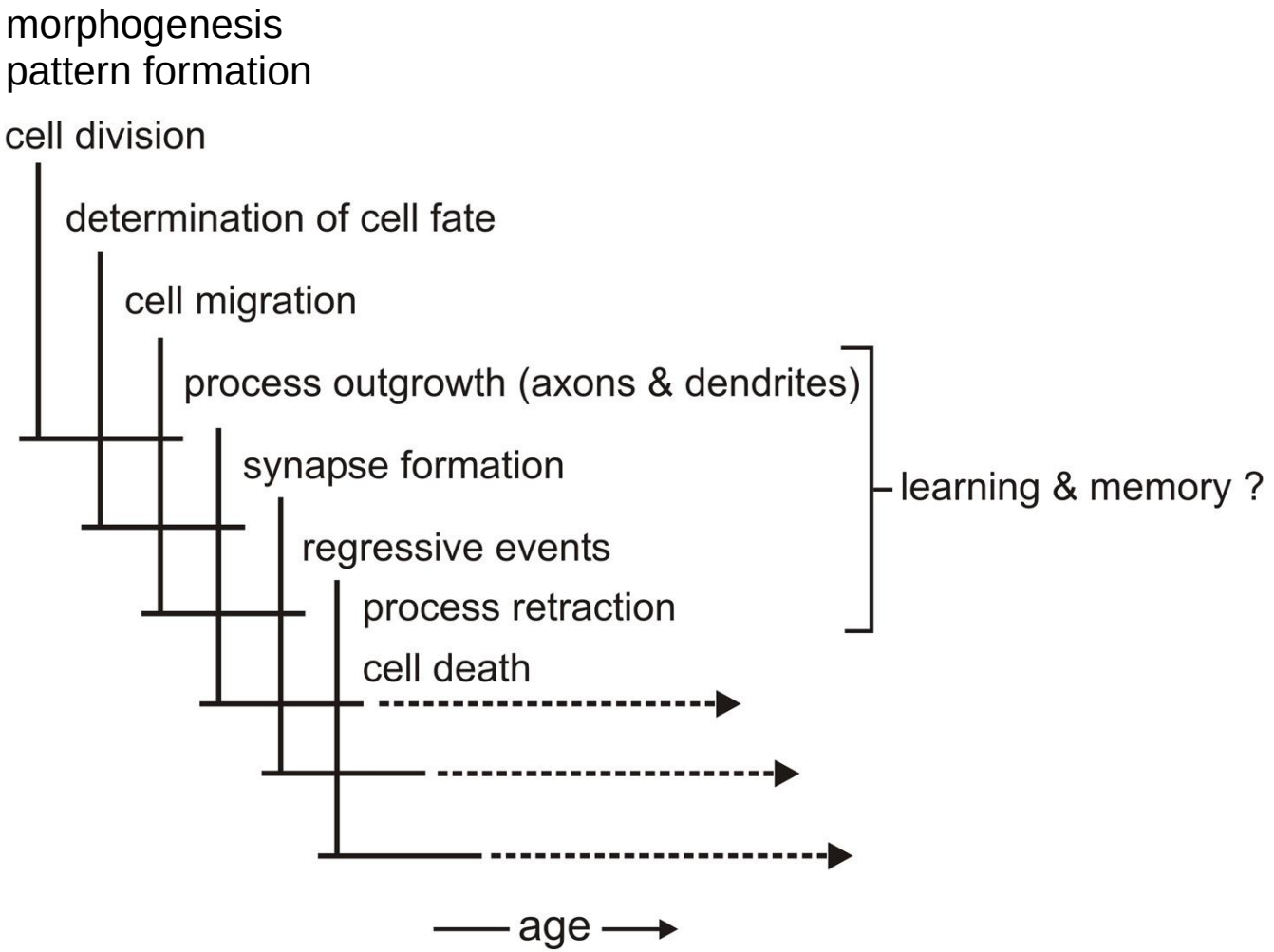
- Causes of disorders of neurodevelopment:
  - Genetic
  - Nutrition
  - Oxygen (high or low)
  - Toxin (teratogen)
  - Infectious disease
  - Trauma
  - Sensory deprivation

Disorders of Nervous System Development

- Every gene involved in nervous system development presumably has been mutated in the human population. Probably most mutations have no effect on development. However, some mutations are lethal, and others result in abnormal development.

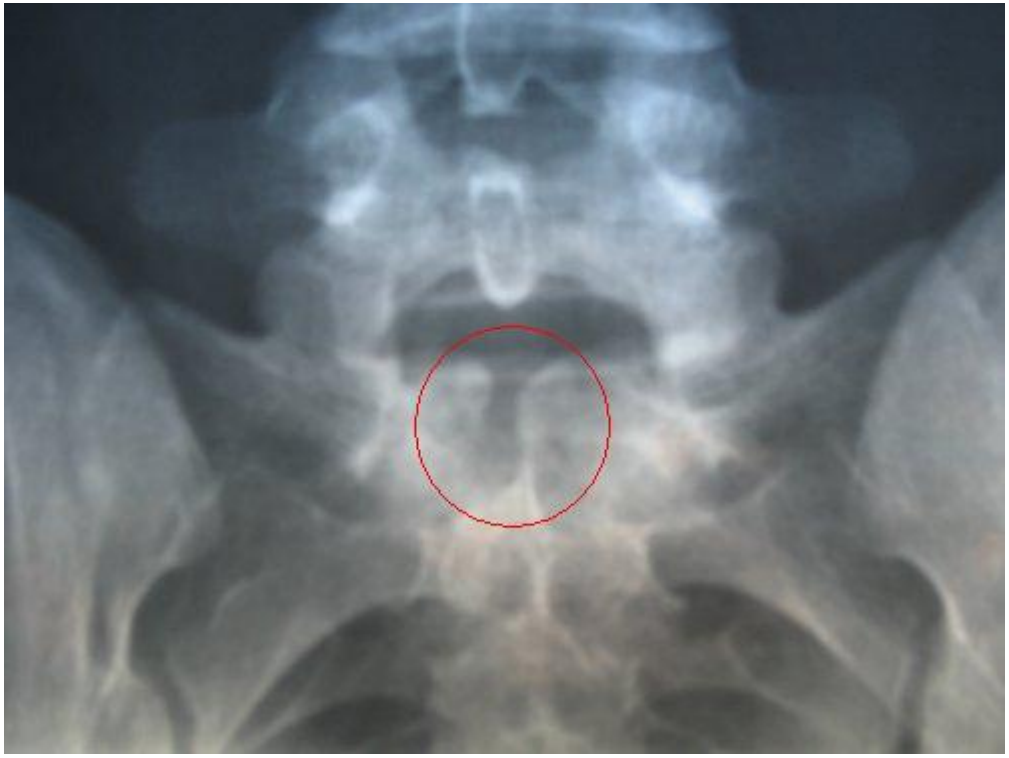
Disorders of Nervous System Development

- Any of the cellular processes we have studied can go wrong and result in developmental disorders.



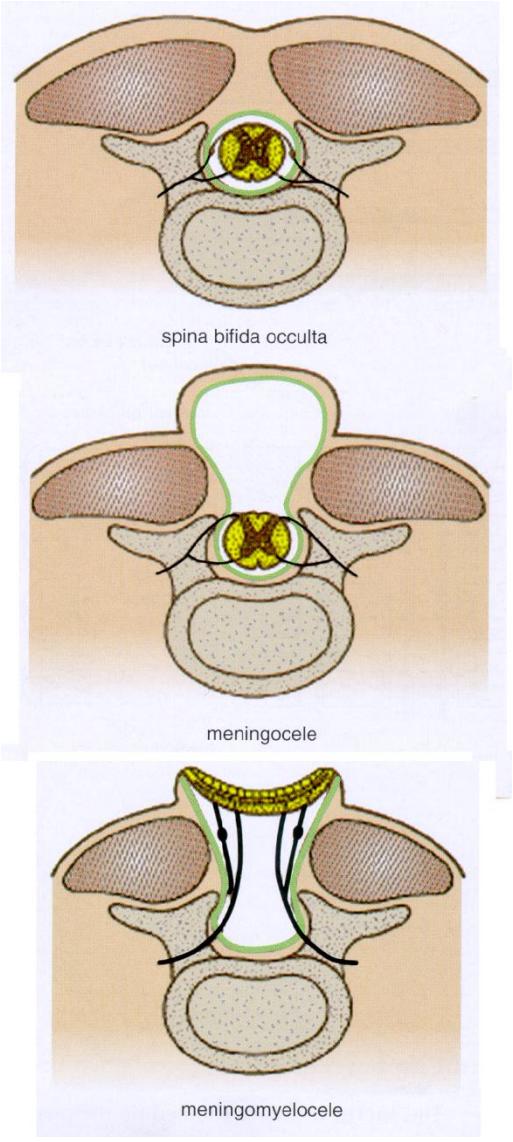
Problems with Morphogenesis

- Spina bifida:
  - Incomplete closure of the spinal neural tube and/or the spine.
  - ~1 in 1000 live births making this one of the most common birth defects.



Problems with Morphogenesis

- Spina bifida (continued):
- Multiple types differing in severity; e.g.:
  - Spina bifida occulta (most common and least severe)
  - Spina bifida cystica
  - Meningocele
  - Meningomylocele (most severe)



Problems with Morphogenesis

- Spina bifida (continued):

- A daily supplement of folic acid (vitamin B9) in the diet of pregnant mothers reduces the incidence of spina bifida by over 70%.

- Folic acid is essential for DNA replication and repair.

- A recent study found that FOLR1, a folic acid binding protein, is expressed by cells in the lateral neural plate, and is essential for normal neural tube closure. FOLR1 interacts with certain cell adhesion molecules. (Balashova et al., 2018)

Problems with Morphogenesis

- Spina bifida (continued):

  The incidence of spina bifida in the adult population is lower than in the newborn population, suggesting that some cases may be due to slow development.

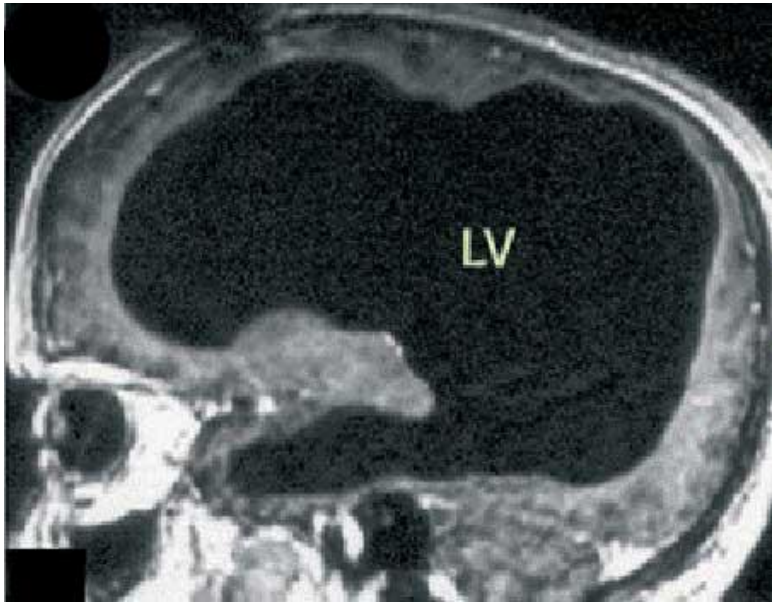
  [73% of people with spina bifida develop an allergy to latex.]

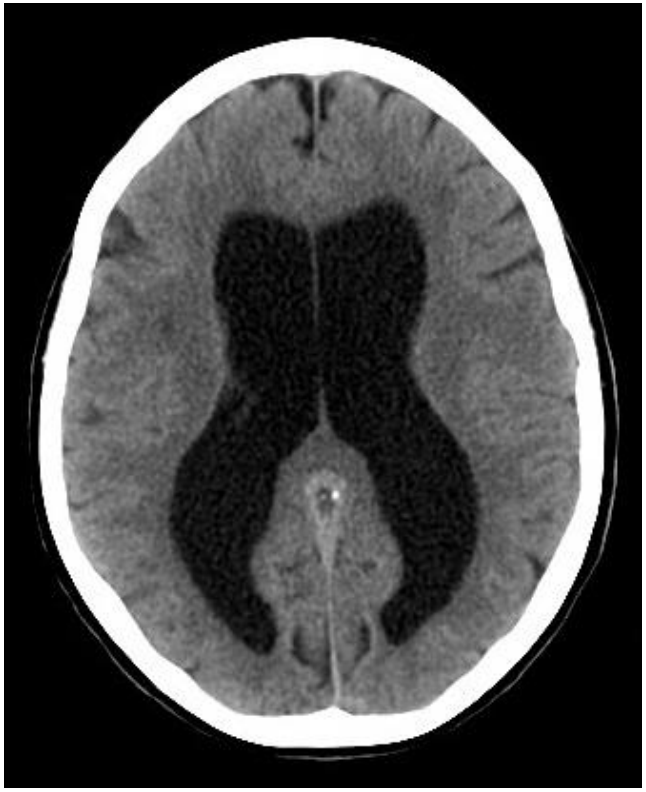
Problems with Morphogenesis

- Anencephaly = incomplete closure of the brain end of the neural tube
- Rare and typically lethal.

Problems with Morphogenesis

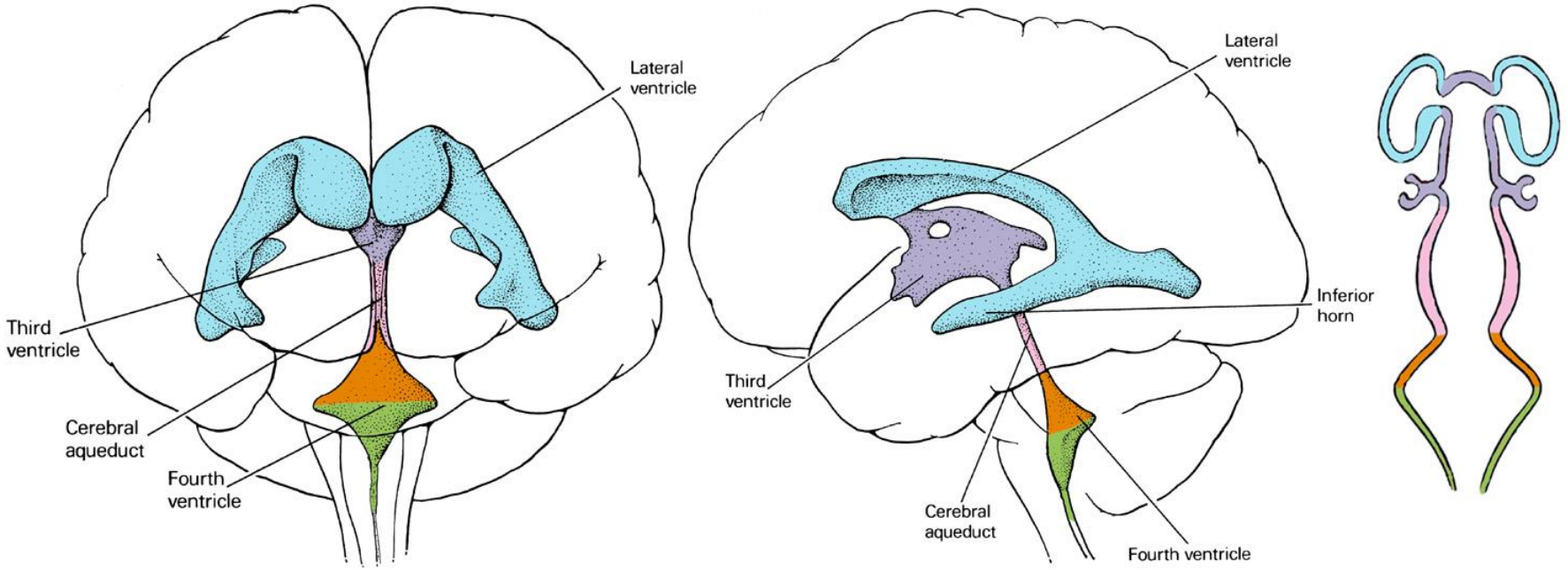
- Hydrocephalus:
  - Insufficient drainage of cerebral spinal fluid (CSF) from the ventricular system of the brain.
  - Increase intracerebral pressure results in increased volume of the ventricles and thinning of the cortex.
  - Often associated with mental retardation.
  - ~1 in 5000 live births
  - Easily corrected by surgery.





Problems with Morphogenesis

- Hydrocephalus (continued):
  - Often due to a restriction in the cerebral aqueduct.



Problems with Morphogenesis

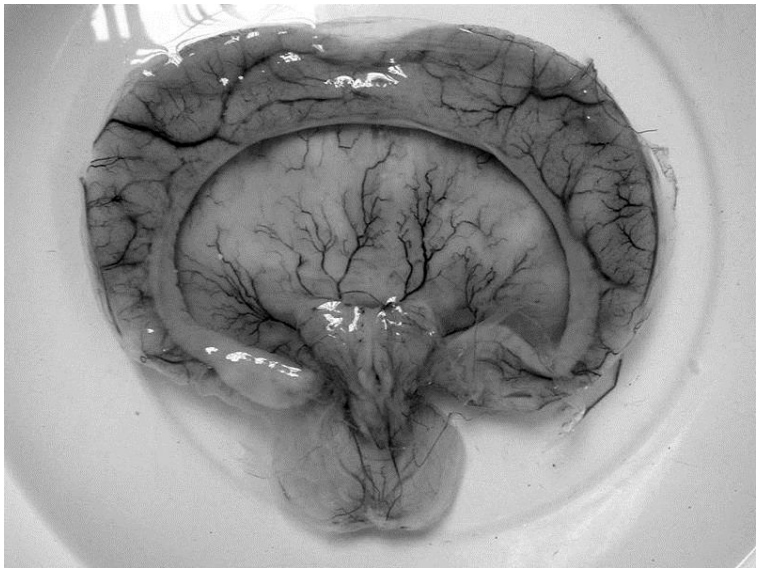
- Hydrocephalus (continued):
- Sometimes caused by a mutation in the gene for the L1 cell adhesion molecule.
- Also caused by infection, trauma or other factors.

Problems with Pattern Formation

- Waardenburg syndrome
- Hearing loss, craniofacial abnormalities and spina bifida.
- ~1 in 42,000
- Caused by an inherited dominant mutation of the Pax3 or Pax6 gene.

Problems with Pattern Formation

- Holoprosencephaly – reduced Shh signaling
- In the most severe cases, the two telencephalic vesicles fail to split resulting in a single cortical hemisphere. Also, the frontal eye fields can fail to split resulting in a cyclops phenotype.
- ~1 in 250 in early embryos; ~1 in 16,000 live births making this the most common forebrain malformation.
- Caused by a missense mutation of the sonic hedgehog gene.

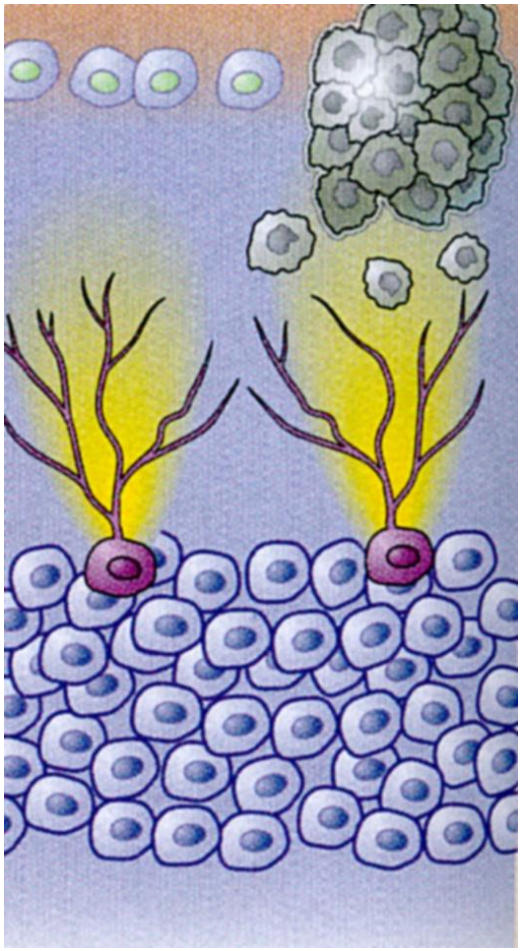


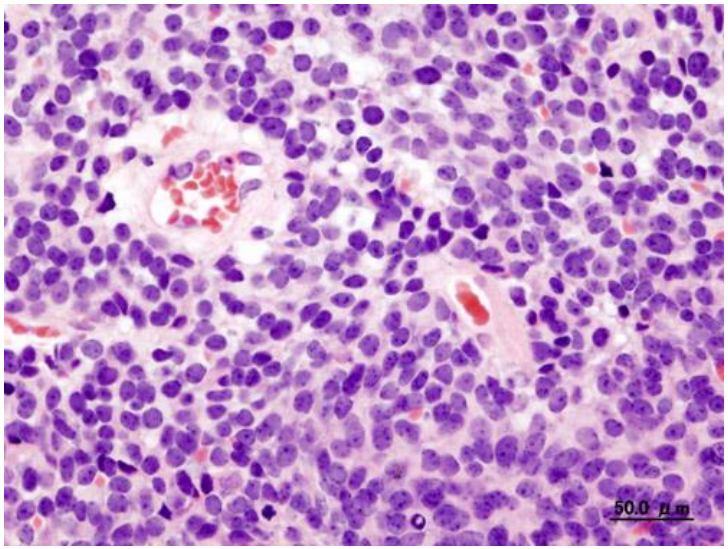
Problems with Pattern Formation

- Holoprosencephaly
- Also, it can be caused by a loss of function mutation in the Zic2 gene, which encodes for a zinc finger transcription factor important in patterning the nervous system.

Problems with Cell Division

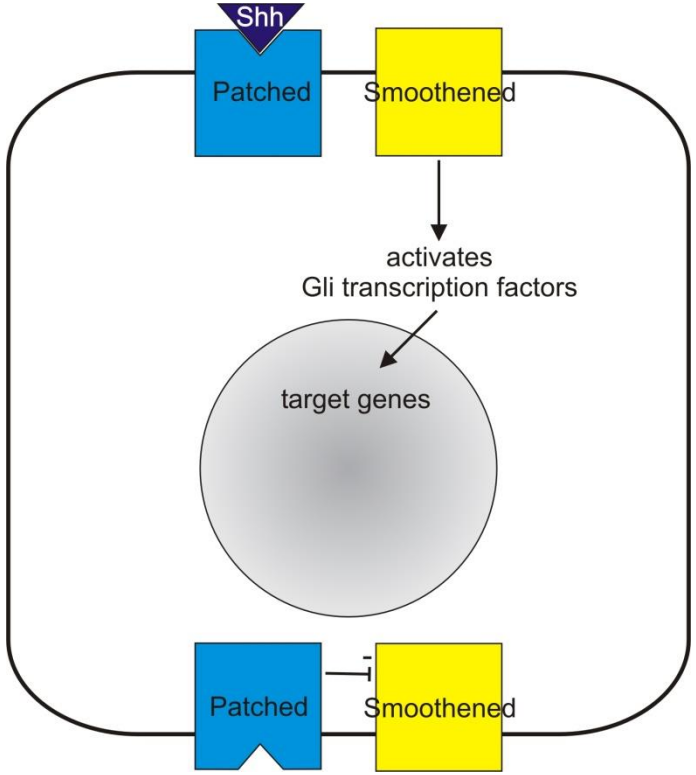
- Medulloblastoma – too much Shh signaling
- Excess division of external granule layer cells of the cerebellum. They move to the outside surface of the developing cerebellum and form tumors.
- ~1 in 100,000 making it the most common developmental brain tumor (although rare). Can manifest up to puberty.
- ~50% do not survive even with medical intervention.





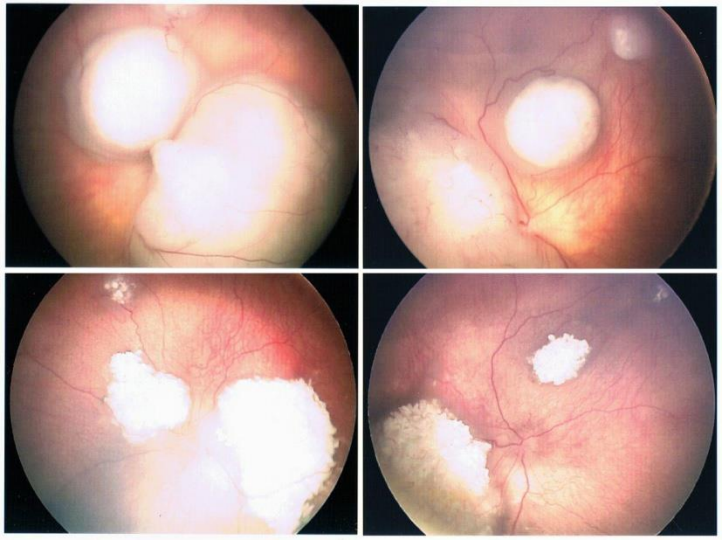
Problems with Cell Division

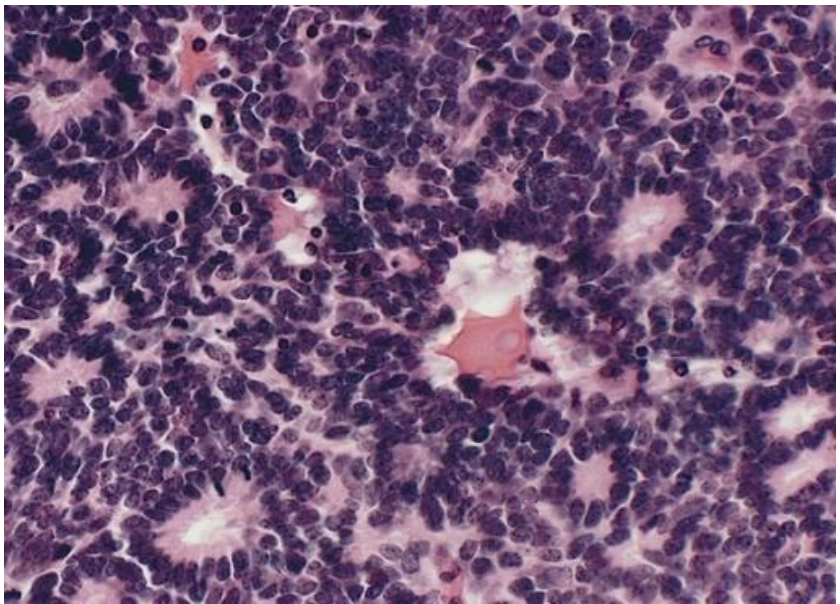
- Medulloblastoma – too much Shh signaling
- Caused by mutations in a component of Shh signaling pathway such as loss of function of Patched, mutations that result in constitutive activation of the Shh pathway.



Problems with Cell Division

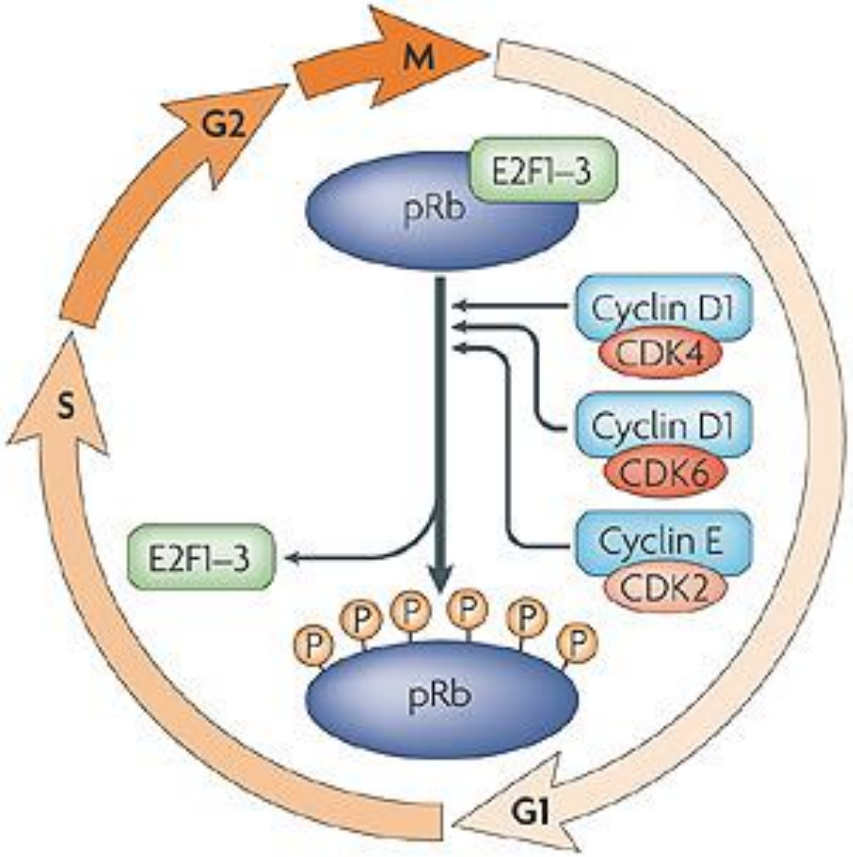
- Retinoblastoma:
- Rapidly developing childhood cancer of the retina.
- ~1 in 15,000 children (most before 1 year of age)
- Treatment by chemotherapy, radiation, cryotherapy or surgery is >95% successful.
- Caused by an inherited mutation of the Retinoblastoma Protein (Rb) gene.
- ~50% of those carrying the mutation will have the disease.





Problems with Cell Division

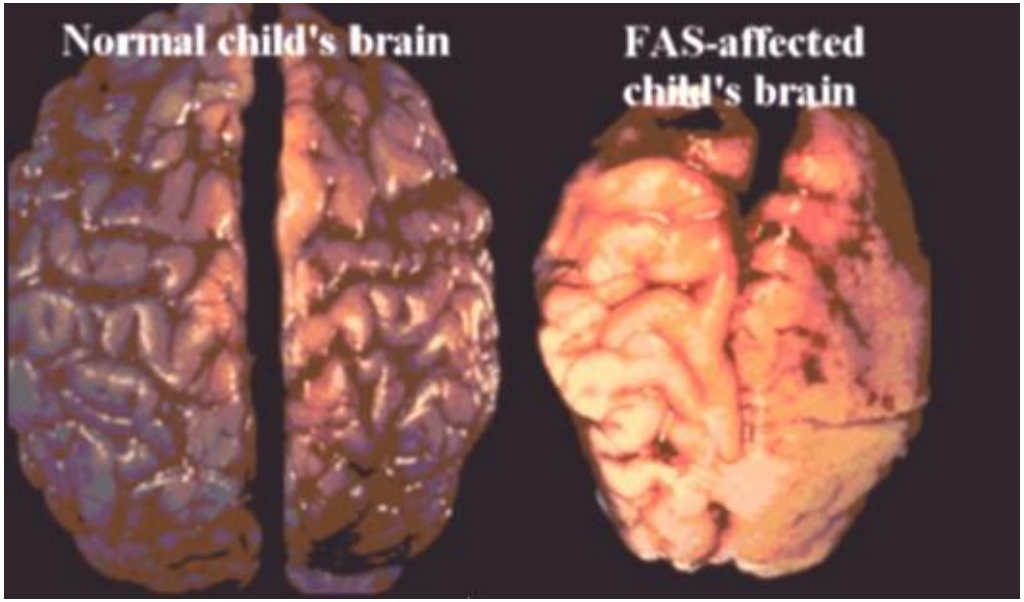
- Retinoblastoma (continued):
- Rb blocks cell division.



Problems with Cell Division

Fetal alcohol syndrome:

- Reduced size of all parts of the nervous system. However, the cortex often shows the greatest effect.
- Leading cause of mental retardation!
- Identifiable disease in ~1 in 500 live births!
- Caused by consumption of alcohol by the pregnant mother. Certain stages of development are more sensitive than others.
- High alcohol levels at critical times in development result in reduced cell division, increased cell death and impaired cell migration in the brain.



Problems with Cell Division

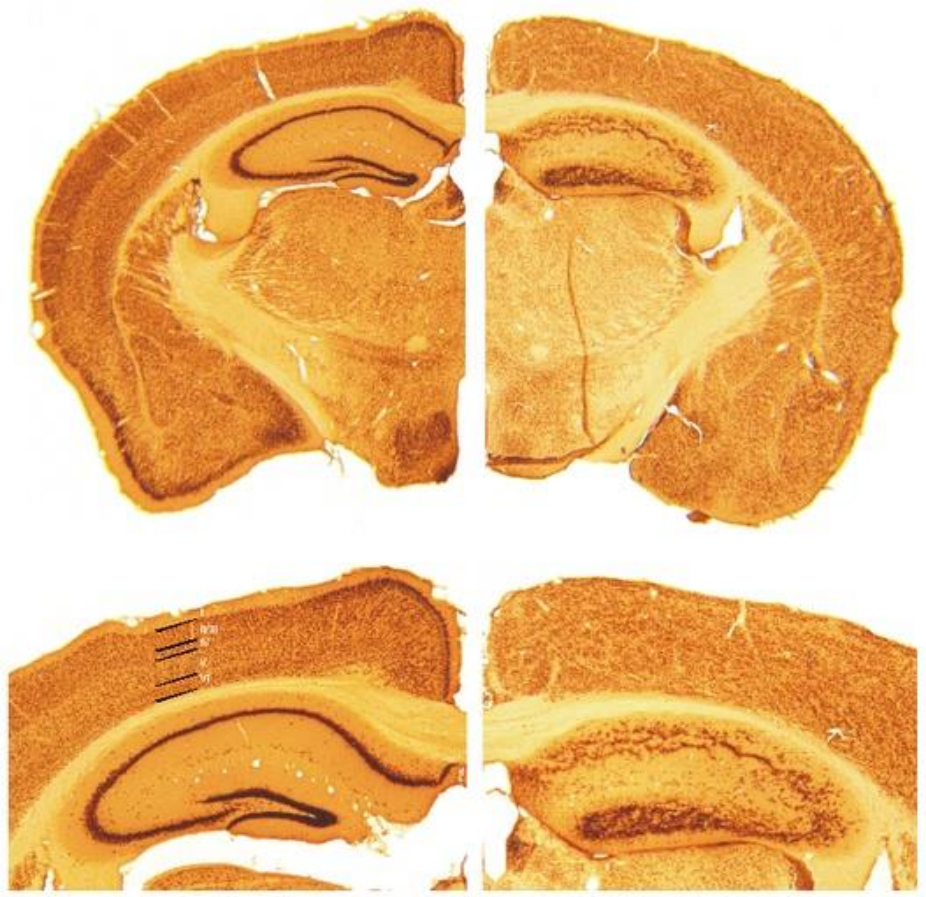
- Low oxygen during birth

Problems with Cell Migration

- Mutations of many of the genes involved in cell migration have been linked to abnormal brain development.

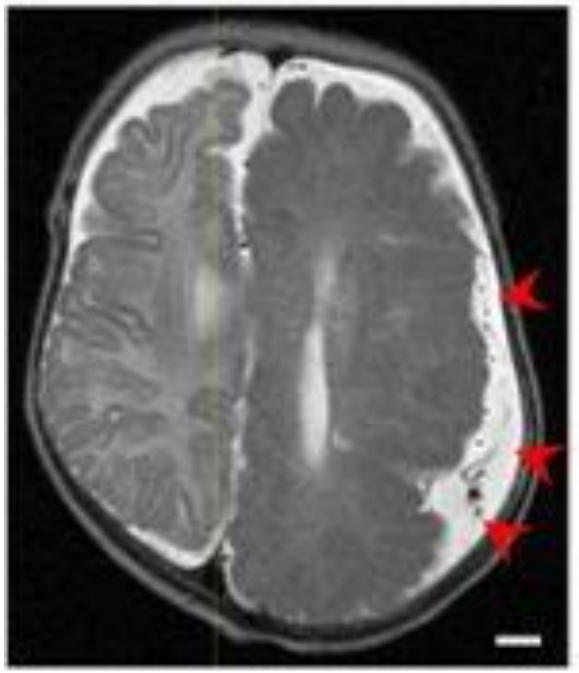
Problems with Cell Migration

- Reeler (CNS)
- Cortical layers are inverted, and there are abnormalities in lamination of cerebellum and many other brain regions.
- Caused by mutation of the reelin, β3 integrin or Disabled-1 genes.



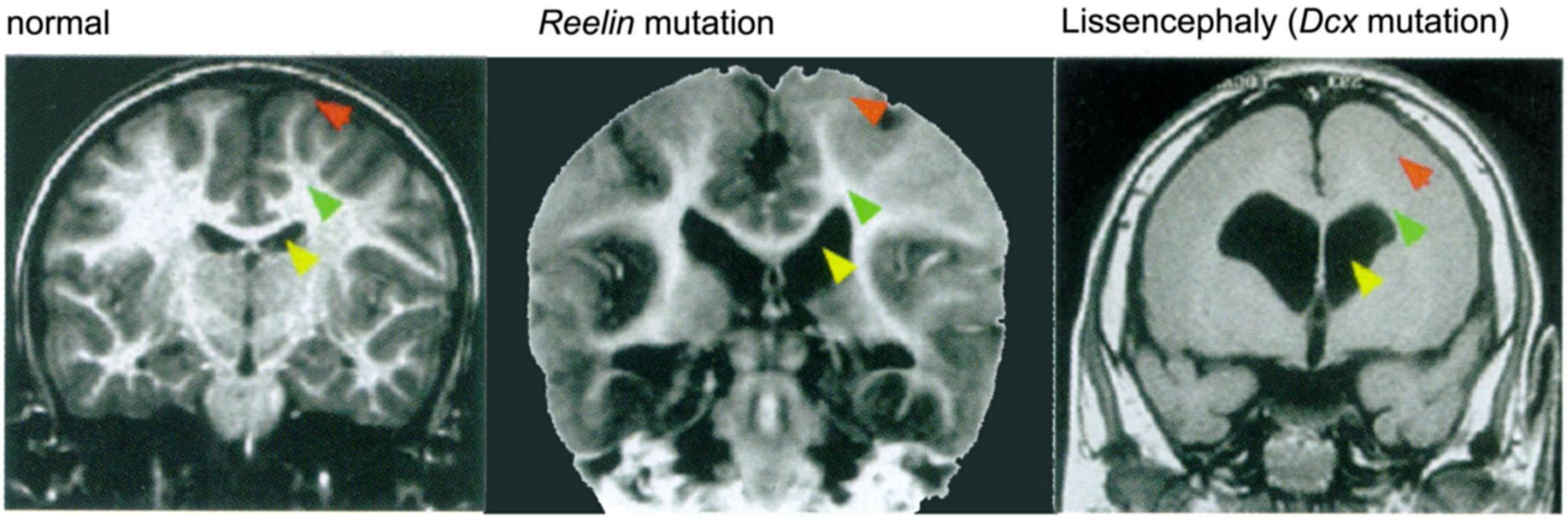
Problems with Cell Migration

- Mutations in Reelin have been observed in humans as well.



Problems with Cell Migration

- Lissencephaly (smooth cortex)
- Cortex is thick, and layers are not obvious.
- Double cortex syndrome or the presence of hetertopias is a less severe form of lissencephaly.
- Females are more often affected than males.
- The more severe migration abnormalities result in mental retardation and motor problems including epilepsy.

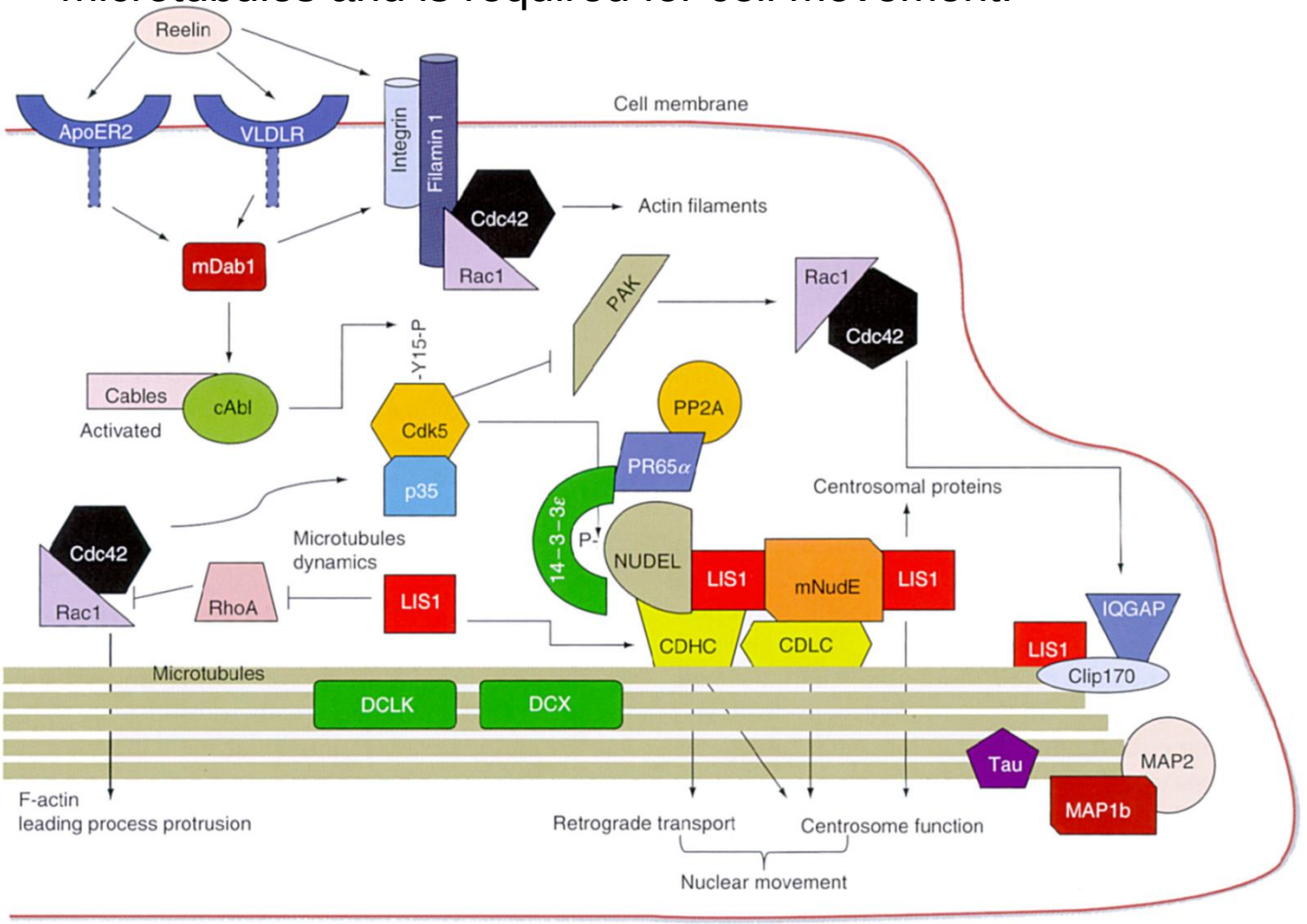


Problems with Cell Migration

- Lissencephaly (smooth cortex)
- Caused by mutation of the Lissencephaly 1 (LIS1) gene or Doublecortin (DCX) gene; mutations are loss-of-function and are a mixture of stop mutations and missense mutations.
- DCX is X-linked gene, which explains why it manifest more often in women. In men, it is presumably lethal.
- LIS1 and DCX are expressed by migrating neurons in the developing brain.

Problems with Cell Migration

- LIS1 is a G-protein that regulates numerous proteins involved in cell movement.
- DCX is a microtubule associated protein that stabilizes microtubules and is required for cell movement.



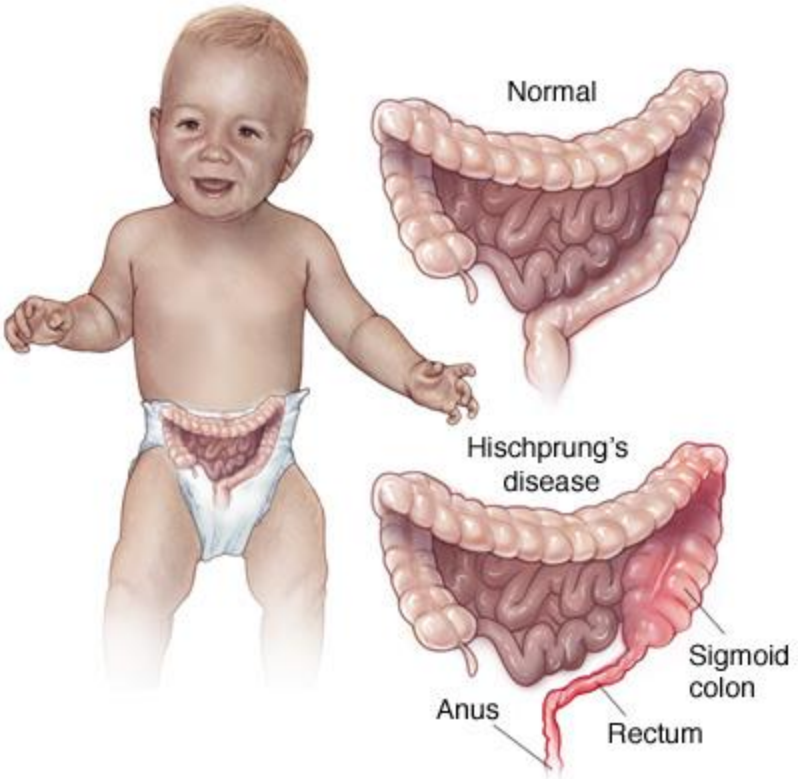
Embryology of Neural Crest

- Neural crest (NC) cells from different rostral-caudal levels give rise to different tissues:
  - Cranial NC cells (from diencephalon to 3rd somite) give rise to many tissues of the head including neurons and glia.
  - Cardiac NC cells (from hindbrain to 4th somite) give rise to the septa of the heart.
  - Enteric NC cells (from 1st to 7th somites) give rise to the entire enteric nervous system.
  - Trunk NC cells (from 4th to 37th somites) give rise to most sensory and autonomic ganglion neurons, glia of the PNS, endocrine cells of the adrenal gland and melanocytes.

(The 1st somite is at the level of the hindbrain.)

Problems with Cell Migration

- Hirschsprung's disease or aganglionic megacolon (PNS)
- Failure of neural crest cells to migrate to the large intestine. Thus, the enteric ganglia do not form in the wall of the intestine, and the intestine is not innervated.
- Without normal innervation, the intestinal muscle does not have peristalsis (i.e. results in bowel obstruction).
- ~1 in 5,000 live births; 5x more common in males than females.
- Caused by a dominant mutation of the Ret gene, which encodes for the GDNF receptor, as well as other genes involved in GDNF signaling.

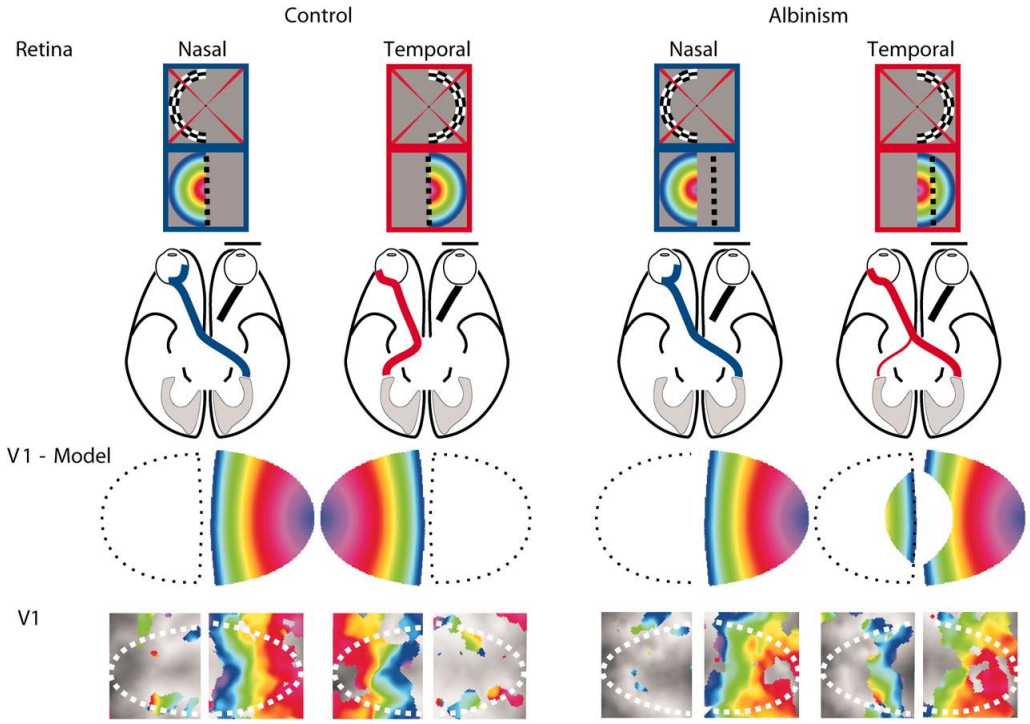


Problems with Axon Guidance

- Oculocutaneous albinism:
  - Caused by a hereditary recessive mutation of the tyrosinase gene or P gene, which results in the lack of melanin.
  - ~1 in 15,000 people have the most common form.

Problems with Axon Guidance

- Oculocutaneous albinism (continued):
  - Hypersensitivity to light due to the lack of pigment in the retinal pigment epithelium.
  - The retinal projection to the brain has an abnormal decussation pattern. More retinal axons cross at the chiasm than in normal individuals. This results in reduced visual acuity and poor stereopsis.



Problems with Axon Guidance

- Duane syndrome:
- Aberrant guidance of cranial nerve axons to the extraocular muscles, which results in a failure to maintain conjugate gaze in all directions.
- Numerous mutations have been documented with the most common in the SALL4 gene, a transcription factor.
- Rare. 10% of the cases are inherited, most are spontaneous.

10 yr old girl with lack of innervation to the lateral rectus muscle for the left eye.

Problems with Synapse Formation

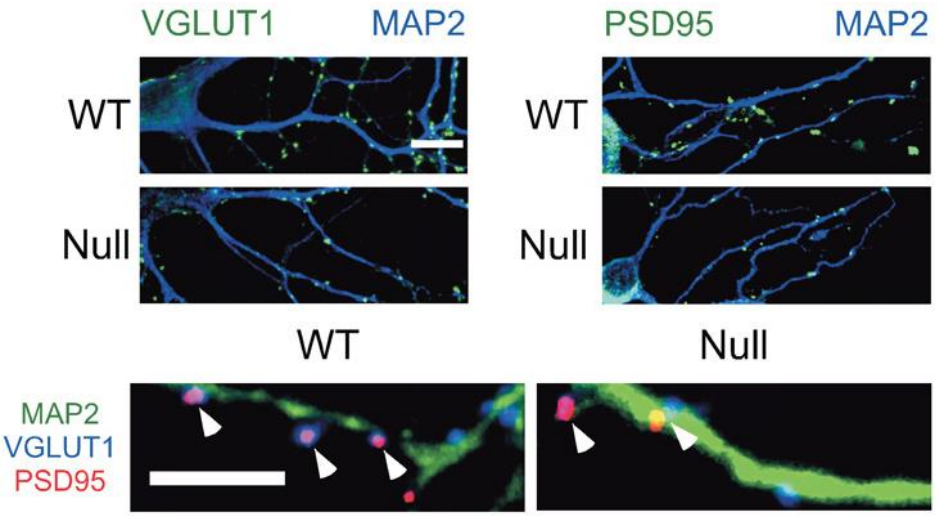
- Rett Syndrome:
- Characterized by:
  - loss of motor control, particularly hands & arms
  - loss of language
  - learning difficulties
  - decelerated head growth
- Onset of symptoms typically between birth and 3 yrs.
- ~1 in 10,000 live births; only females; believed to be embryonic lethal for males or affected males die young.

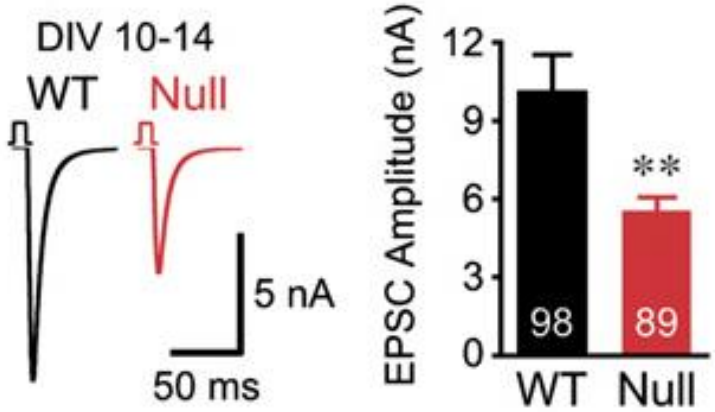
Problems with Synapse Formation

- Rett Syndrome (continued)
- genetic; X-linked recessive
- mosaic chromosomal inactivation allows female to survive
- ~1% passed from parent; most are spontaneous mutations.
- loss of function mutation in methl-CpG-binding protein 2 (MeCP2) gene
- MeCP2 is a transcriptional repressor; it forms a complex with CREB to bind the promoter domain of CREB target genes.
- Mice expressing mutant MeCP2 have the same symptoms as humans.

Problems with Synapse Formation

- Rett Syndrome (continued)
- Mice with a knockout of MeCP2 have fewer synapses in the cerebral cortx and reduced excitatory postsynaptic potentials.





Chao et al., 2007, Neuron 56:58

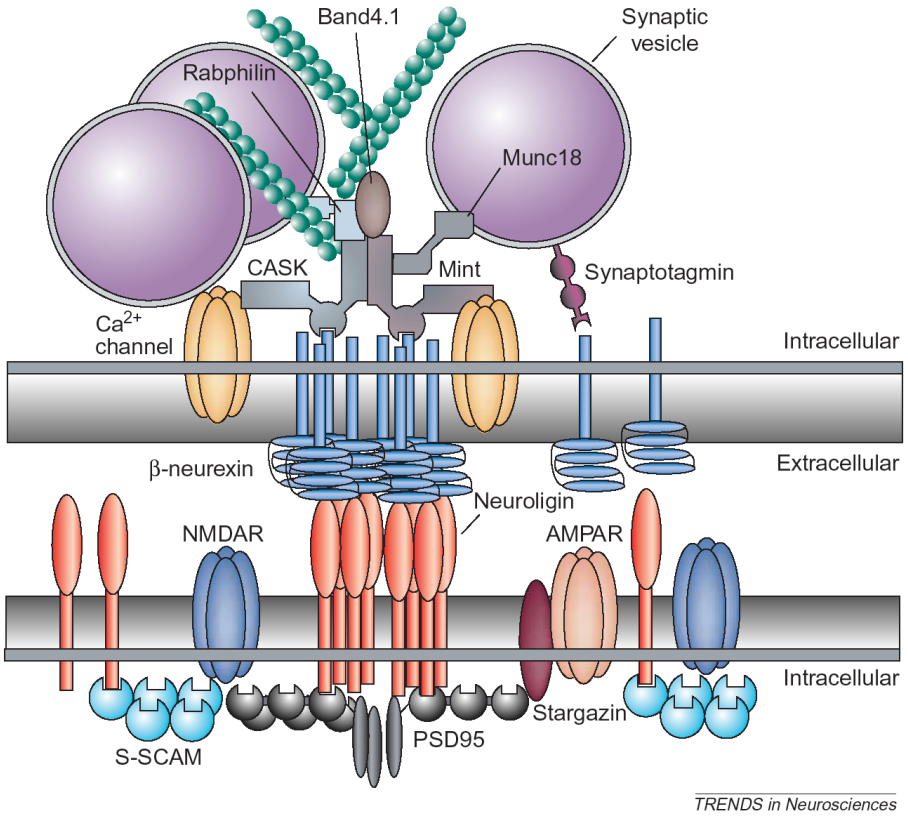
Problems with Synapse Formation

- Autism (autism spectrum disorders)
  - Difficulty with social interactions
  - ~1 in 1,000 children
  - There is some evidence for reduced inhibitory activity in certain higher brain centers in affected individuals.
  - There is strong evidence for a genetic component to the disease.
  - 4-8 times more frequent in males than females, which suggests that it is an X-linked trait.
  - Many candidate genes including several involved in synapse formation such as neuroligin, several involved in Wnt signaling such as frizzled, and several involved in neurotransmission such as GABA.

Synapse Assembly

- As the synapse matures, adhesion in the active zone is mediated by neurexin (presynaptic) and neuroligin (postsynaptic). These integral membrane proteins anchor a number of synaptic scaffolding proteins inside the cell (via PDZ domains).

  e.g. Neuroligins bind PSD95 (and other related scaffolding proteins); PSD95 binds neurotransmitter receptor proteins.



Problems with Synapse Formation

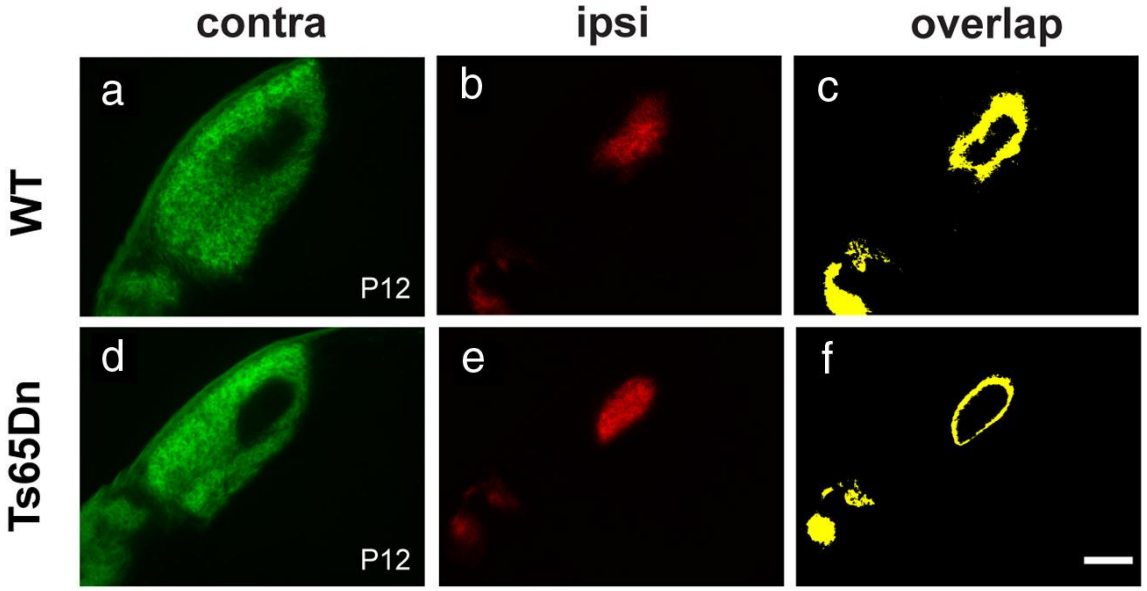
- Autism (autism spectrum disorders)
  - A recent study in monkey showed that over expression of MeCP2 resulted in autism-like behavior. (Liu Z, et al., 2016, Nature)

Problems with Refinement of Connections

- Down Syndrome (Trisomy 21)
  - Characterized by mental retardation and frequently epilepsy, as well as a number of other problems. Usually short in stature with a characteristic ‘Downs’ face.
  - ~1 in 800 children; chance increases with older mothers.
  - The most common cause of mental disability.
  - Due to an extra chromosome 21.

Problems with Refinement of Connections

- Down Syndrome (Trisomy 21)
  - Studies in mice suggest that refinement of connections is too fast and too.
  - The cell adhesion molecule, DSCAM, is on this chromosome, and animal studies indicate that DSCAM is part of the phenotype.



Blank M et al. (2011)

Problems with Refinement of Connections (or maybe Myelination)

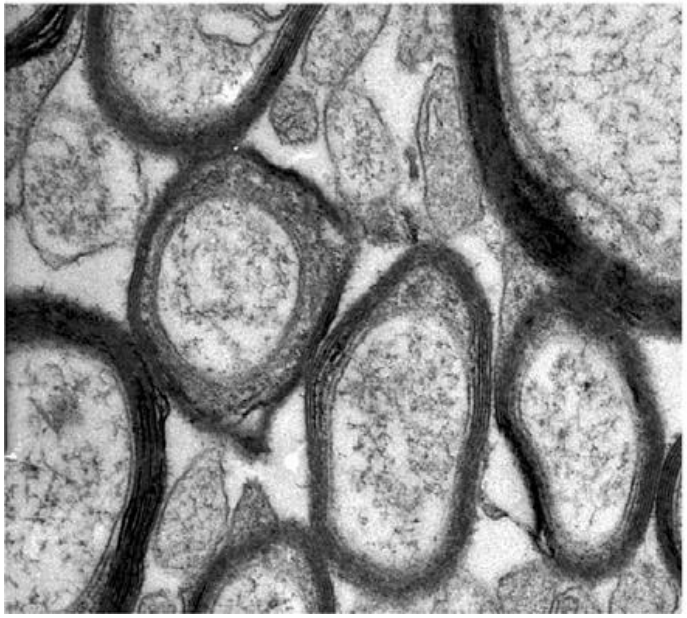
- Down Syndrome (Trisomy 21)

Neuron *89*, 1-15 (2016)

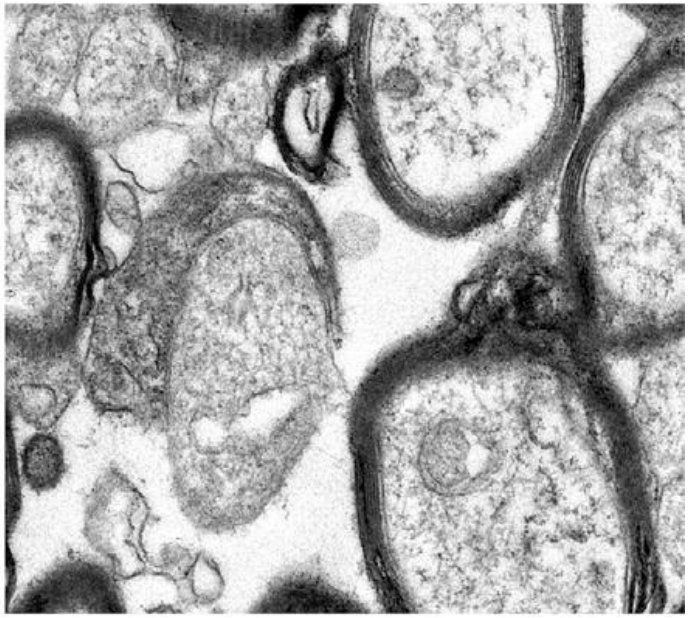
Down Syndrome Developmental Brain Transcriptome Reveals Defective Oligodendrocyte Differentiation and Myelination

Jose Luis Olmos-Serrano,[1,9] Hyo Jung Kang,[2,3,9] William A. Tyler,[1,9] John C. Silbereis,[2,9] Feng Cheng,[2,4] Ying Zhu,[2] Mihovil Pletikos,[2] Lucija Jankovic-Rapan,[2] Nathan P. Cramer,[5] Zygmunt Galdzicki,[5] Joseph Goodliffe,[1] Alan Peters,[1] Claire Sethares,[1] Ivana Delalle,[6] Jeffrey A. Golden,[7] Tarik F. Haydar,[1,*] and Nenad Sestan[2,8]

Control



Ts65Dn (hypomyelination)



Problems with Refinement of Connections

- Fragile-X Syndrome:
- Most common cause of genetically linked mental retardation.
- Individuals have mild to severe mental retardation and motor problems (e.g. tremor and ataxia).
- ~1 in 4,000 males and ~1 in 8,000 females.
- Neurons in the brains of affected individuals have abnormal dendritic spines and an increased number of spines and excitatory synapses.

Problems with Refinement of Connections

- Fragile-X syndrome (continued):

- Caused by loss-of-function mutation of the Fragile-X Mental Retardation gene (FMR1) on the X-chromosome.

- Mutation is a CGG trinucleotide repeat expansion. Ten to 40 repeats found in normal individuals. More than 200 repeats are found in people with the full disease.

- FMR1 encodes a cytoplasmic RNA-binding protein that is highly expressed in neurons. ~4% of mRNAs in the brain are bound by FMR1 protein.

- FMR1 regulates microRNAs, which in turn regulate expression of specific proteins.

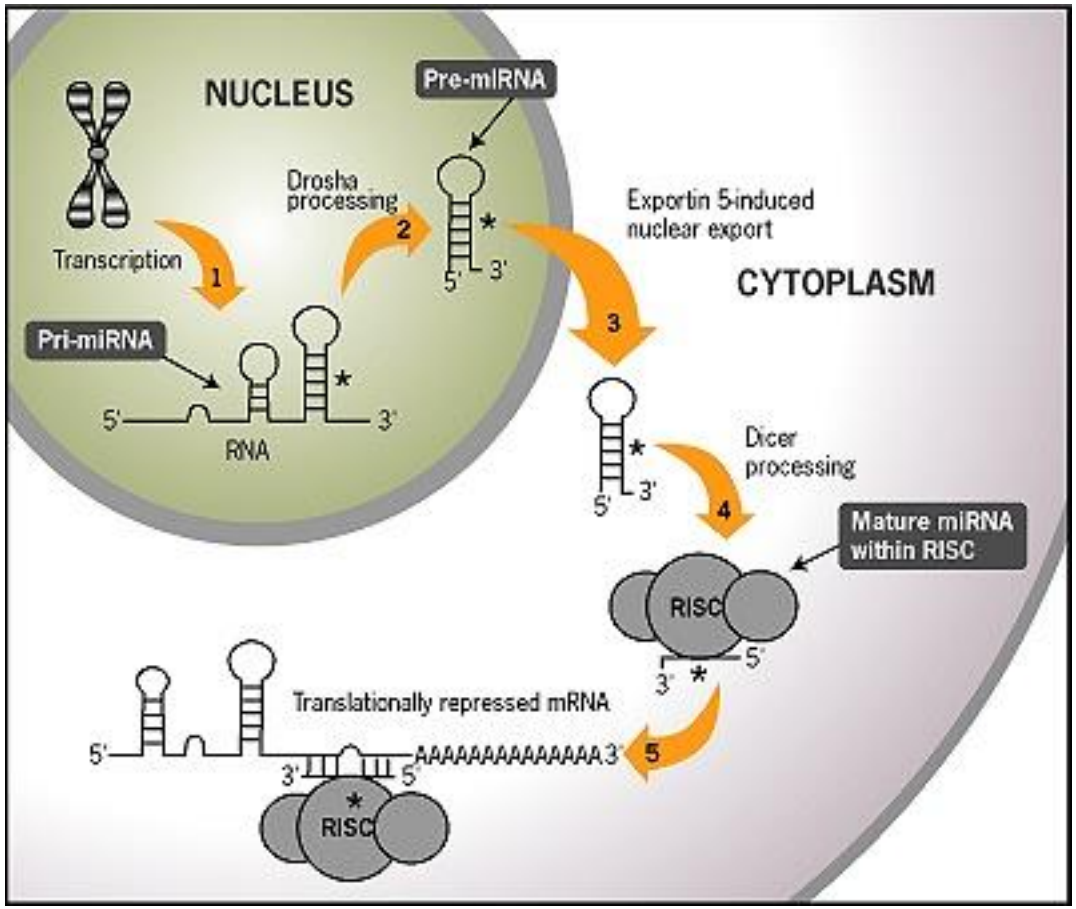
Problems with Refinement of Connections

- Fragile-X syndrome (continued):
  - FMR1 functions in the postsynaptic cell, and is required for normal synapse elimination during development.
  - Although the RNA-binding is required for FMR1 function, it is unclear how it is involved in synapse elimination.

Problems with Refinement of Connections

- MicroRNAs:

- MiRNAs are non-coding RNAs, 18-25 nucleotides long. MiRNAs are cleaved from longer RNAs in a multi-step process. MiRNAs hybridize with mRNA, thus blocking translation.



Problems with Refinement of Connections

- MicroRNAs (continued):
  - Most of the 462 miRNAs identified (in humans) so far are expressed in the brain, and most of these are developmentally regulated.
  - MiRNAs have an essential role in cell fate, process growth and synapse formation during development.
  - In the adult, miRNAs are involved in learning and memory.

Problems with Refinement of Connections

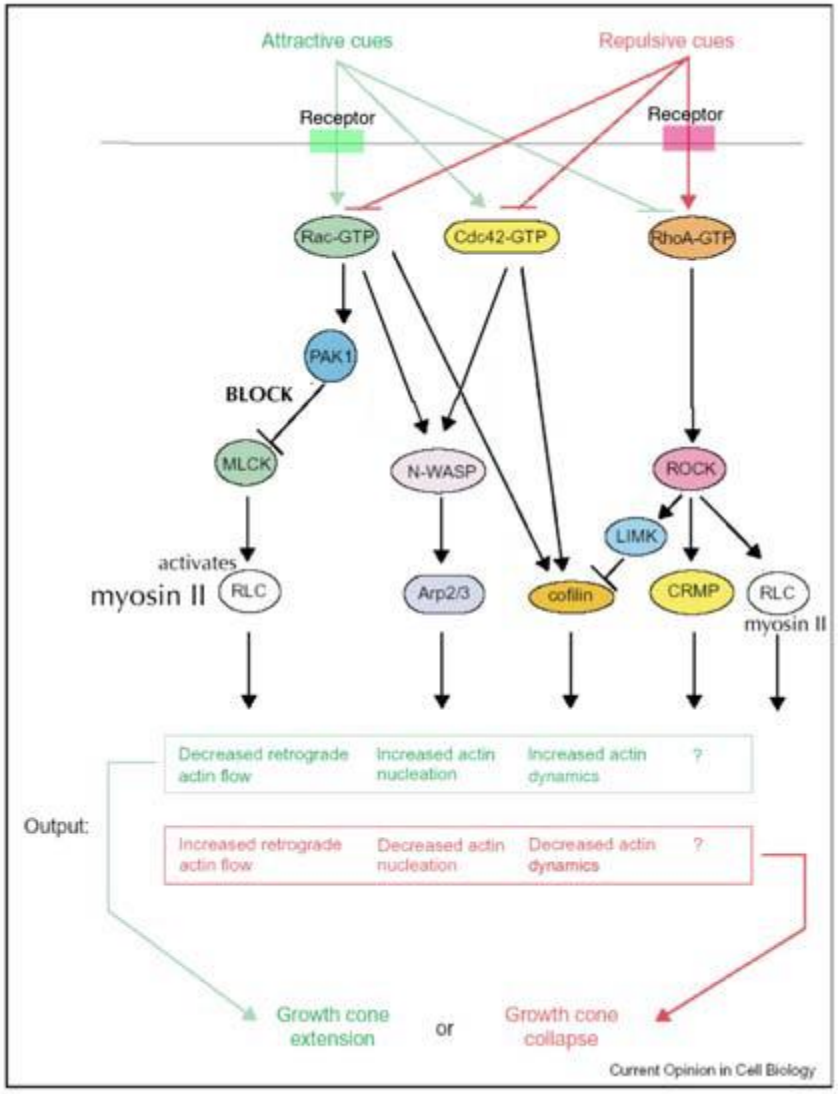
- MicroRNAs and Fragile X syndrome:
- miR-134 is localized to cortical dendrites; it's function is regulated by synaptic activity.
- miR-134 blocks expression of the protein kinase, Lim Kinase-1; LimK correlates with dendritic spine maintenance; miR-134 correlates with fewer spines.

Growth Cone Dynamics

Activation of RhoA in growth cones induces growth cone collapse and axon retraction.

LimK phosphorylates and inhibits cofilin, which stabilizes actin.

-Paul Letourneau



Problems with Refinement of Connections

- MicroRNAs and Fragile X syndrome:
  - Wildtype FMR1 is associated with polysomes at synapses.
  - FMR1 is part of the RISC complex, which is required for miRNA function.