Developmental Genetics

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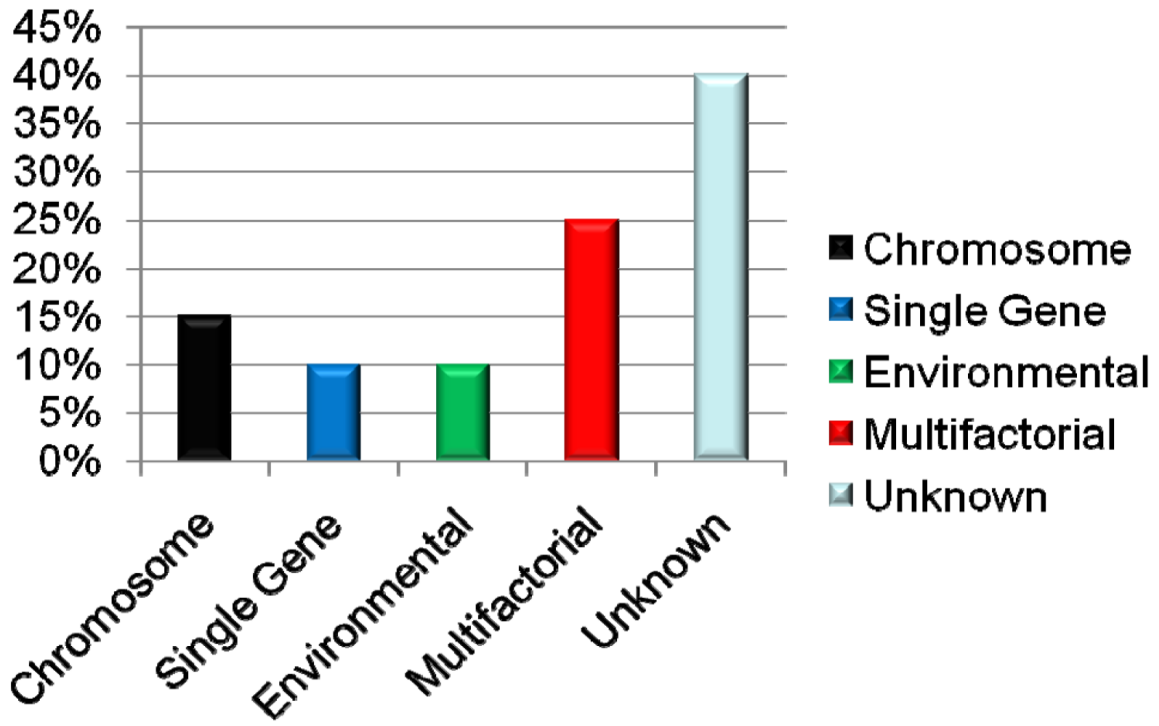
Congenital Anomalies

- 1-3% of all newborns
- Leading cause of neonatal morbidity and mortality
  - 20% of infant deaths
  - 10% NICU admissions, 25-35% of deaths
- Pediatric admissions
  - 25% to 30% have major birth defect

Causes of Congenital Anomalies

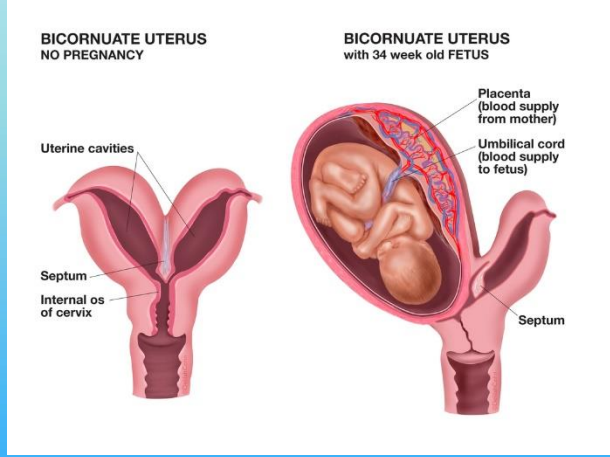


Congenital Anomalies

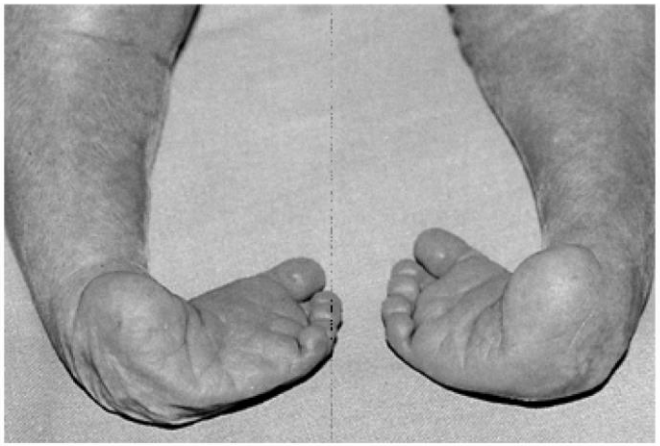
Isolated Anomaly	Incidence per livebirths
Undescended testes	1:30
Heart defect	1:150
Club foot	1:300
Neural tube defects	1:500
Cleft lip ± cleft palate	1:1000
Hypospadias	1:1000
Polydactyly	1:1500
Cleft palate	1:2000
Craniosynostosis	1:2000
Syndactyly	1:2000

Deformation

- Developmental Process is *normal*
- Mechanical force alters structure
- Examples:
  - Oligohydramnios
  - Breech presentation
  - Bicornuate uterus



DEFORMATION



Clubbed feet

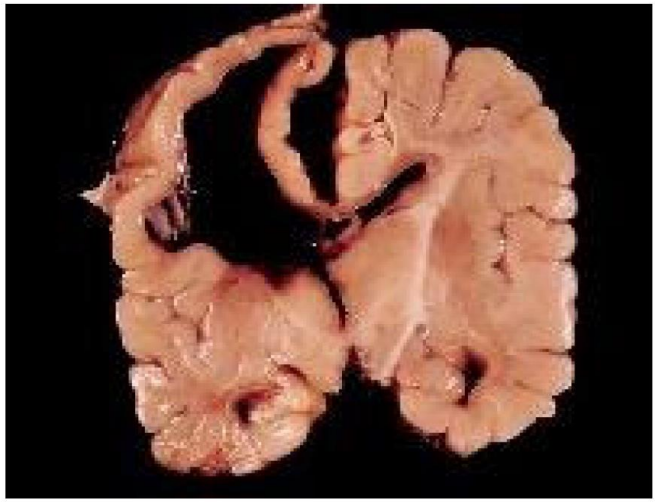
- spina bifida

Moore. The Developing Human. Saunders, 1994

Disruption

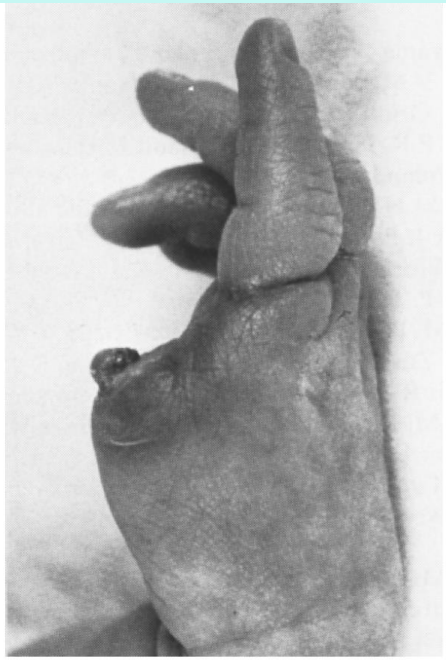
- Developmental process is *normal*, but interrupted
- Examples:
  - Amniotic band sequence
  - Fetal Cocaine exposure

Disruption



Porencephaly

http://www.neuropat.dote.hu/develop.htm#Porencephaly



Amniotic Band

Wiedemann and Kunze. Clinical Syndromes. Mosby-Wolfe, 1997

Dysplasia

- Abnormal tissue organization, microscopic structure
- Examples:
  - Skeletal or connective tissue dysplasias
  - Ectodermal dysplasias

Dysplasia

Ectodermal Dysplasia

Buyse. Birth Defects Encyclopedia. Blackwell Science, 1990;
Baraitser and Winter. Color Atlas of Congenital Malformation Syndromes, Mosby-Wolfe, 1996;
Bergsma. Birth Defects Compendium, Alan R. Liss, 1979.

Malformation

- Morphological defect from an intrinsically *abnormal* developmental process
- Examples: holoprosencephaly, congenital heart disease, neural tube defect

Malformation

Unilateral Cleft Lip and Palate

Moore, Persaud, and Shiota. Color Atlas of Clinical Embryology. Saunders, 1994

Syndrome

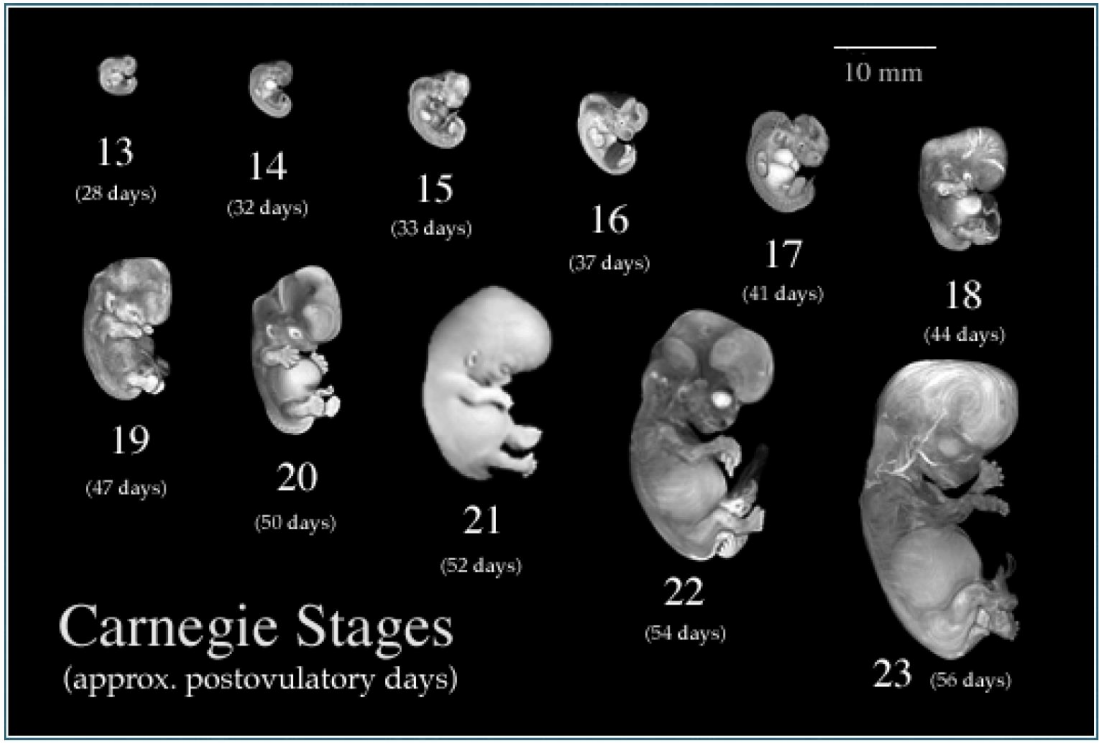
- A recognizable pattern of anomalies presumed to be causally related
  - Genetic: chromosomal, single gene
  - Environmental: alcohol, retinoic acid
  - Complex: more than one genetic and/or environmental factor

Syndrome

- Fetal Alcohol
  - Growth retardation
  - Microcephaly
  - Mental retardation
  - Short palpebral fissures
  - Short nose
  - Smooth philtrum
  - Thin upper lip
  - Small distal palanges
  - Hypoplastic finger nails
  - Cardiac defects

Clarren and Smith. NEJM 298:1063, 1978

Normal Development



http://embryo.soad.umich.edu/carnStages/carnStages.html

Developmental Pathways and Mechanisms

Cellular Processes During Development

Germ Cells and Stem Cells

Fate, Specification and Determination

Axis Specification and Pattern Formation

Positional Information: HOX Clusters

Cellular and Molecular Mechanisms of Development

Developmental Pathways

Evolutionary Conservation of Mechanisms and Pathways

Cellular Processes During Development

Fundamental Problem

Turn a single cell (fertilized egg) into a fully and normally developed organism

Four Basic Cellular Processes During Development

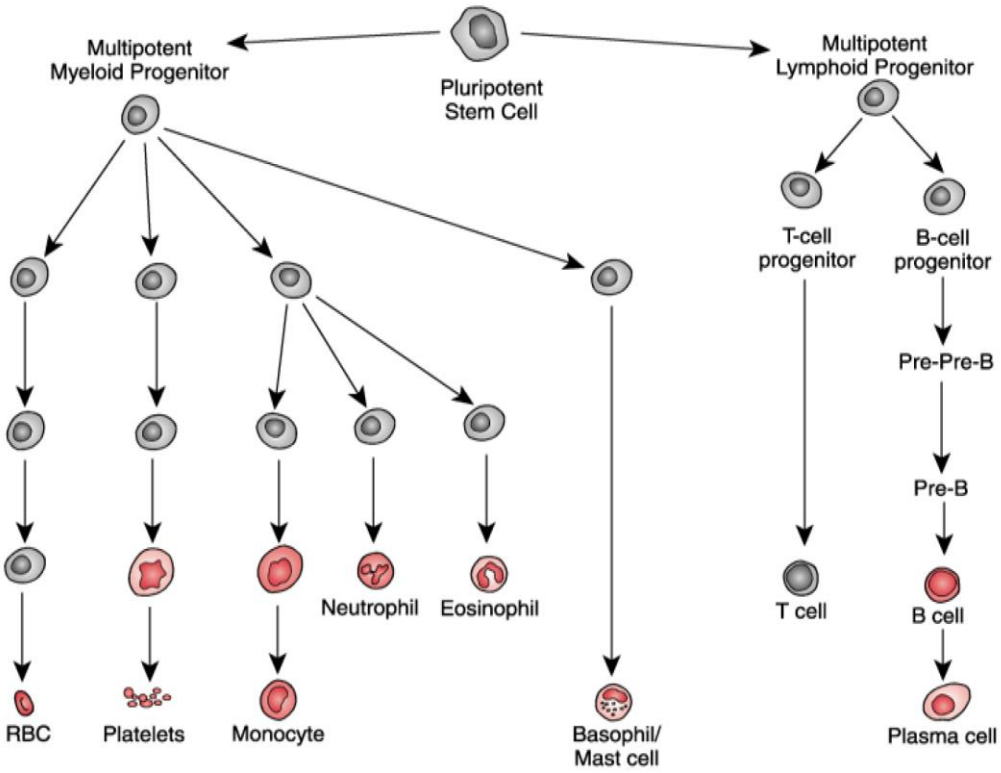
Proliferation (increase cell numbers by division)

Differentiation (acquire novel functions or structures)

Migration (move within the embryo)

Programmed Cell Death (controlled elimination of cells)

Germ Cells and Stem Cells



Fate, Specification, and Determination

Fate: process by which an undifferentiated cell moves through a series of discrete steps in to manifest distinct functions or attributes to become a further differentiated cell (an erythrocyte, a keratinocyte, or a cardiac myocyte).

Specification: when a cell acquires specific characteristics but can still be influenced by environmental cues (signaling molecules, positional information) to change its ultimate fate.

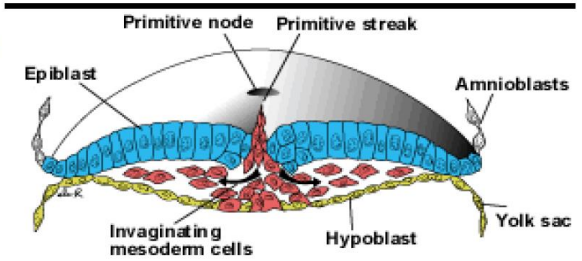
Determination: the state of commitment when a cell either irreversibly acquires attributes or has irreversibly been committed to acquire those attributes.

With the exception of the germ cell and stem cell compartments, all cells undergo specification and determination to their ultimate developmental fate.

Differentiation

CS 7, day 15-17

- Gastrulation occurs as cells migrate from the epiblast, to form mesoderm.
- Mesoderm lies between the ectoderm and endoderm as a continuous layer
- From the primitive node a tube extends under the ectoderm to form the notochord

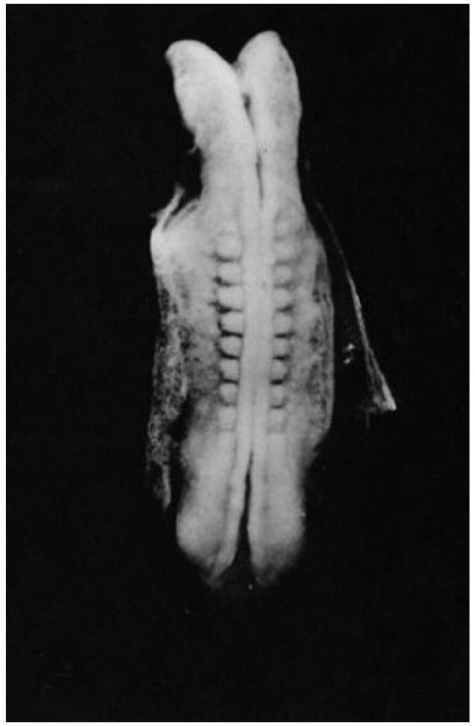


http://www.med.unc.edu/embryo_images/unit-bdyfm/bdyfm_htms/bdyfm003.htm

Pattern Formation

CS 10, week 4

- Ectoderm: Neural folds fuse
- Mesoderm: continued segmentation of paraxial mesoderm (4 - 12 somite pairs)



http://embryology.med.unsw.edu.au/wwwhuman/Stages/Stages.htm

Organogenesis

CS 16, week 6

Nasal pits moved ventrally, auricular hillocks, foot plate

CS 18, week 7

Finger rays, Ossification commences

http://embryology.med.unsw.edu.au/wwwhuman/Stages/Stages.htm

Growth

CS 20, week 8
Upper limbs longer
and bent at elbow

CS 23, week 9
Rounded head,
body and limb

http://embryology.med.unsw.edu.au/wwwhuman/Stages/Stages.htm

Axis Specification

A-P: anterior-posterior (cranial-caudal)

[Proximal-distal for limbs]

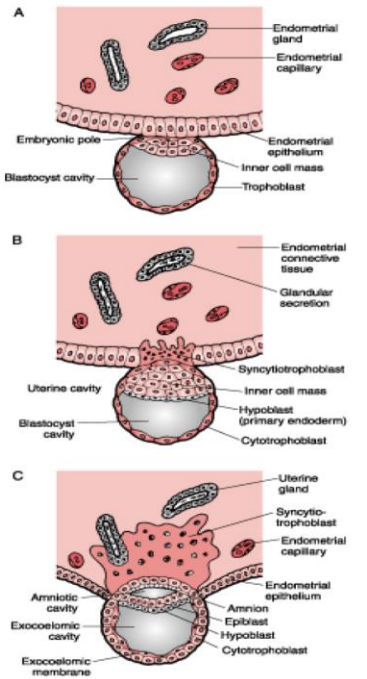
D-V: dorsal-ventral (back-front)

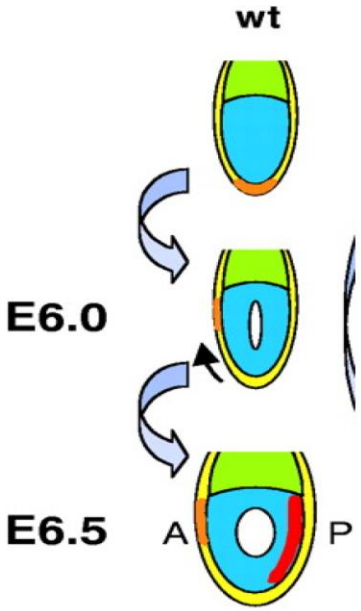
L-R: left-right axes

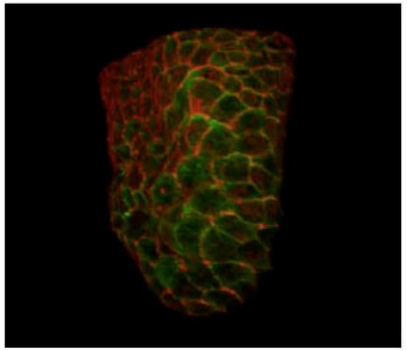
Patterning program of the embryo is overlaid onto these axes

Axis Specification

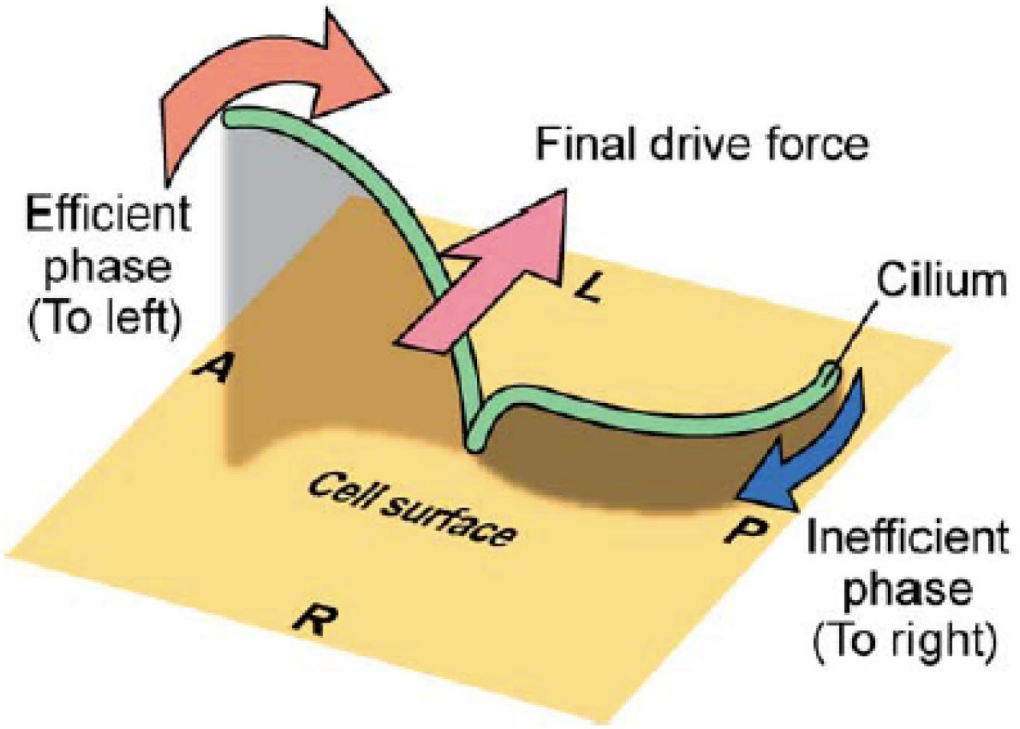
Rotation of the Proximo-Distal (P-D) to Anterior-Posterior (A-P) axis and Mesoderm Induction



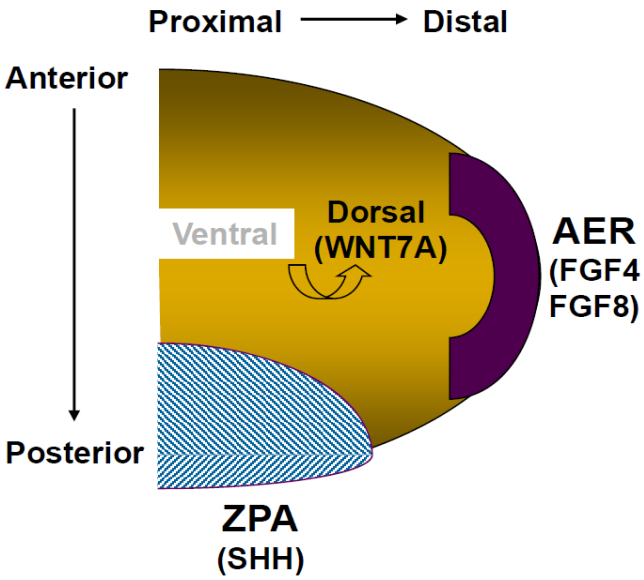




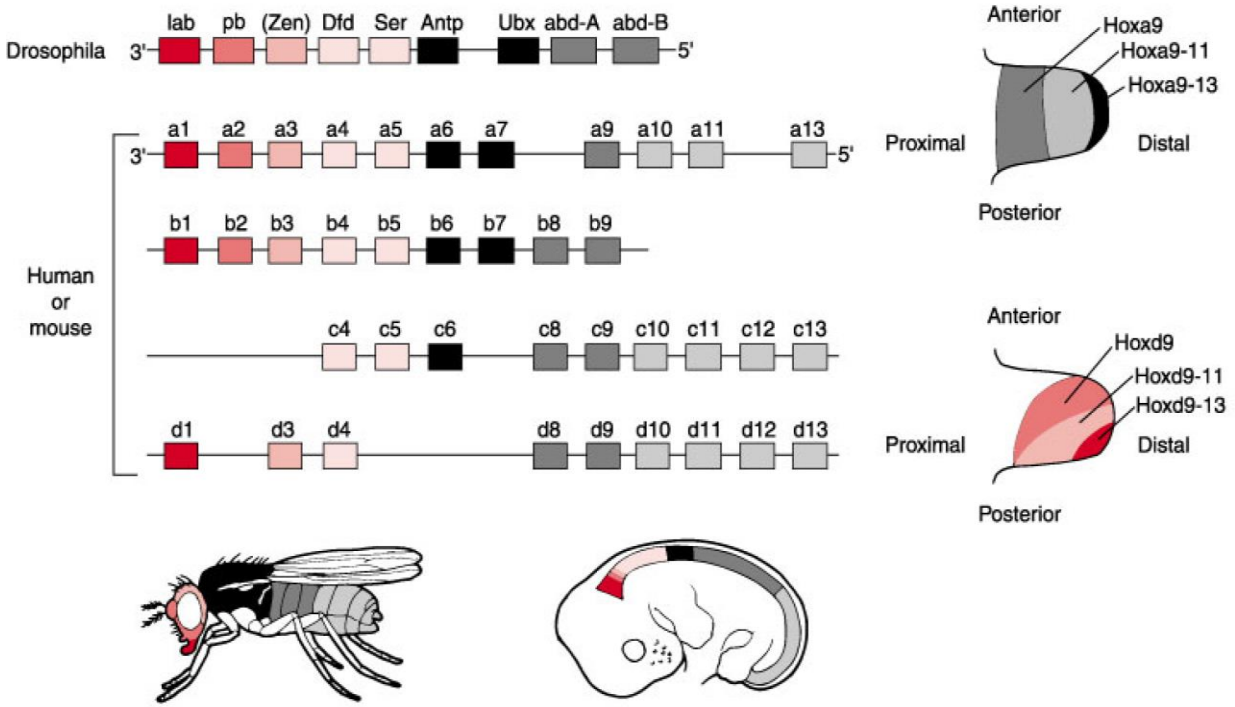
Nodal cilia rotate in a clockwise fashion to drive leftward fluid flow



Nonaka et al. PLoS Biology 3:e268 (2005)


Proximal
Distal
Anterior
Posterior
Ventral
Dorsal
(WNT7A)
AER
(FGF4
FGF8)
ZPA
(SHH)

Positional Information: HOX Clusters



HOX Gene Mutation: Syndromes

- Anterior - Head
  - HOXA1
    - Athabaskan Brainstem Dysgenesis
    - Bosley-Salih-Alorainy Syndrome (Duane Syndrome, Deafness, Delayed Motor Milestones, Autism)
- Posterior - Tail
  - HOXA11
    - Radioulnar Synostosis with Amegakaryocytic Thombocytopenia
  - HOXA13
    - Hand-Foot-Uterus Syndrome
    - Preaxial Deficiency, Postaxial Polydactyly and Hypospadius

HOX Gene Mutation: Syndromes

- Posterior - Tail
  - HOXD10
    - Vertical Talus, Congenital (Rocker-Bottom Foot)
  - HOXD13
    - Synpolydactyly 1 (Syndactyly, Type II)
    - Brachydactyly, Types D and E

Cellular and Molecular Mechanisms of Development

Gene Regulation by Transcription Factors

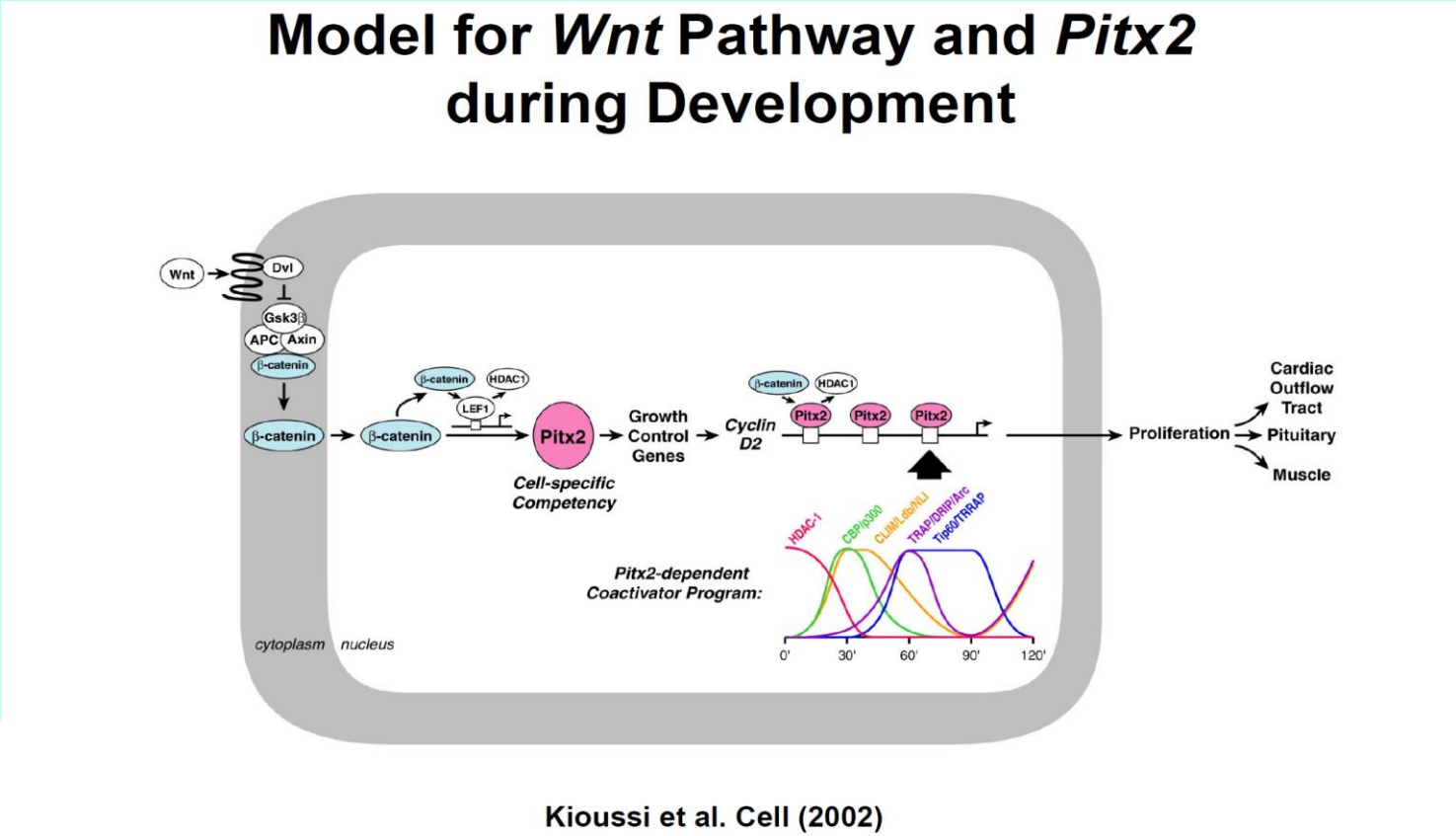
Morphogens and Cell-Cell Signaling

Cell Shape and Organization

Cell Migration

Programmed Cell Death

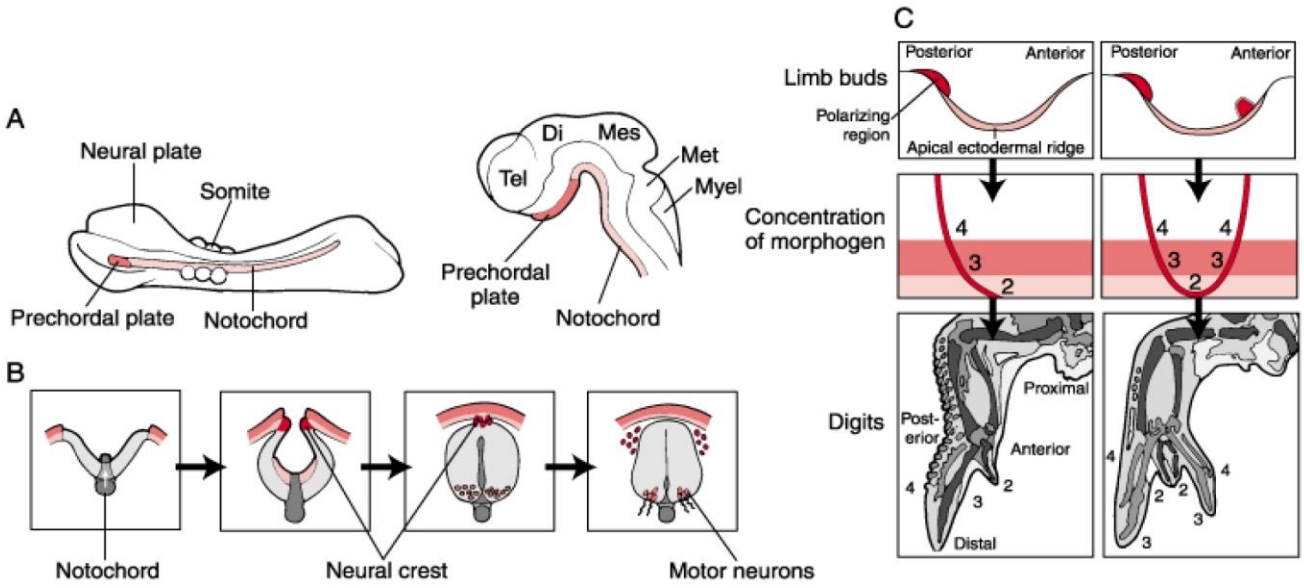
Gene Regulation by Transcription Factors



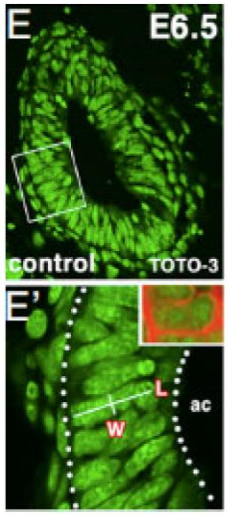
Kioussi et al. Cell (2002)

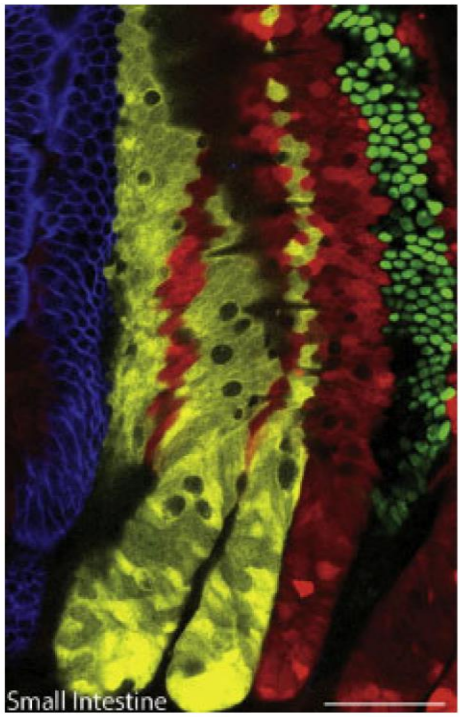
Morphogens and Cell-Cell Signaling

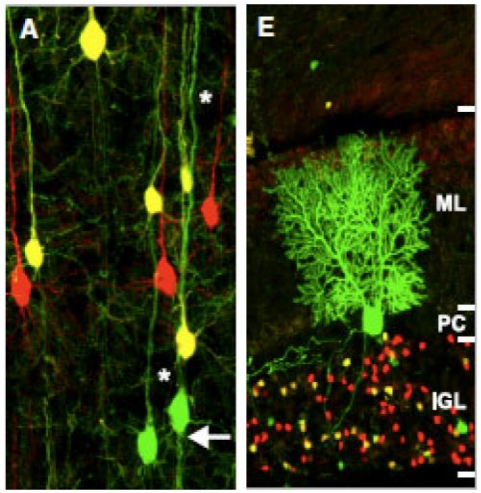
Morphogens: *Sonic Hedgehog* (*SHH*) in Neural Tube and Limb



Cell Shape and Organization

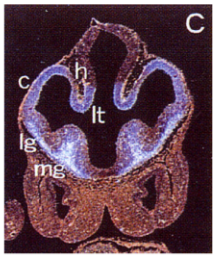


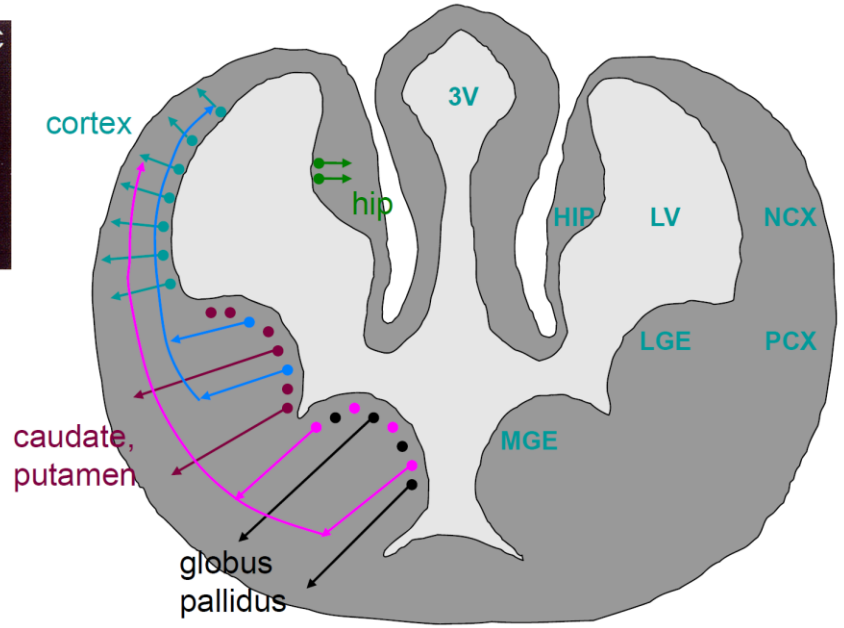




Cell Migration

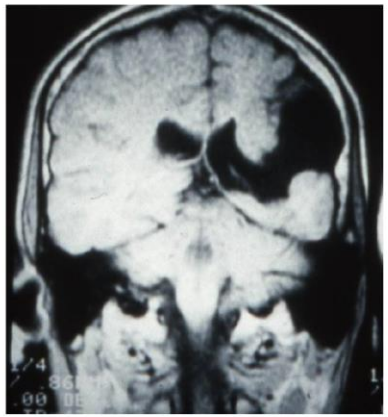
The cortex forms by radial and nonradial migration





Neuronal Proliferation & Migration Syndromes

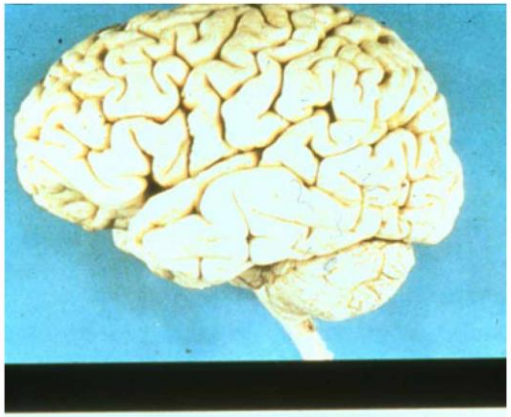
- Proliferation
  - Microcephaly
    - AR – multiple loci
- Migration
  - Lissencephaly
    - Miller-Dieker *LIS1*
    - X-linked: DCX (doublecortin)
    - X-linked with abnormal genitalia (ARX)
    - Cobblestone dysplasia (Fukuyama MD, Walker-Warburg, muscle-eye-brain)
  - Heterotopia
    - Periventricular nodular (*FLN1*)
- Cortical Organization
  - Pachygyria/polymicrogyria
  - Schizencephaly
    - *EMX2*



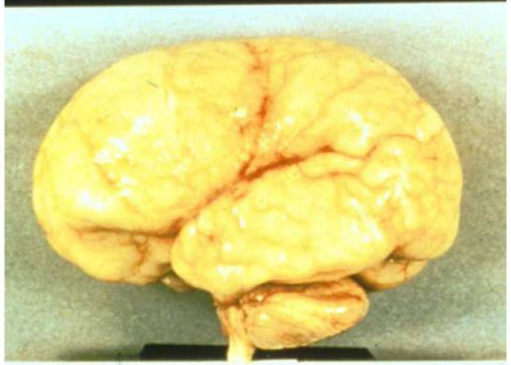
schizencephaly

Lissencephaly - Brain

Normal

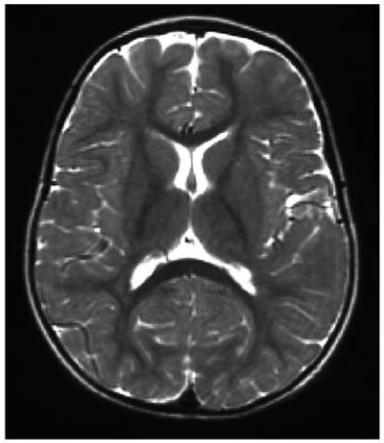


Type I
Lissencephaly
(Severe)

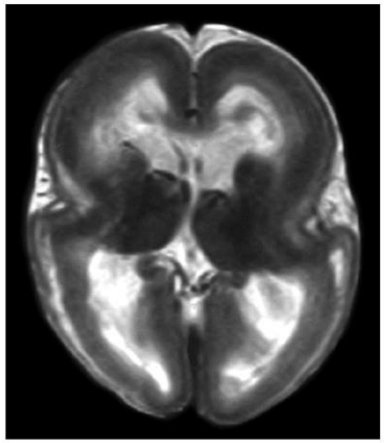


Lissencephaly – Brain MRI

Normal

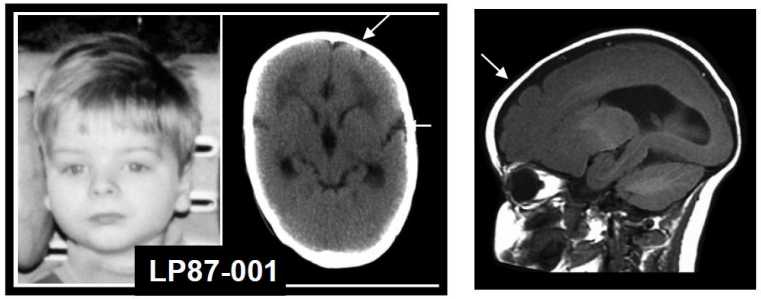


Lissencephaly
Severe MR
Seizures
Early Death

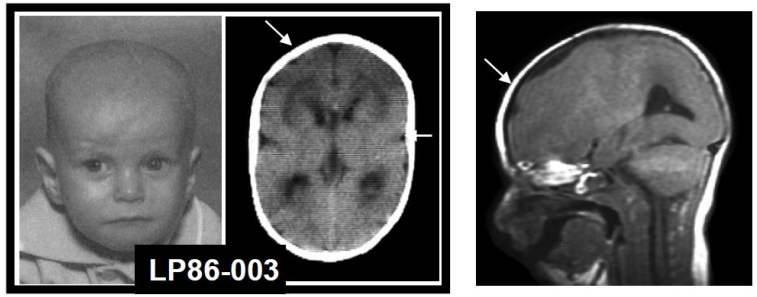


Incidence: 1/50,000-1/100,000

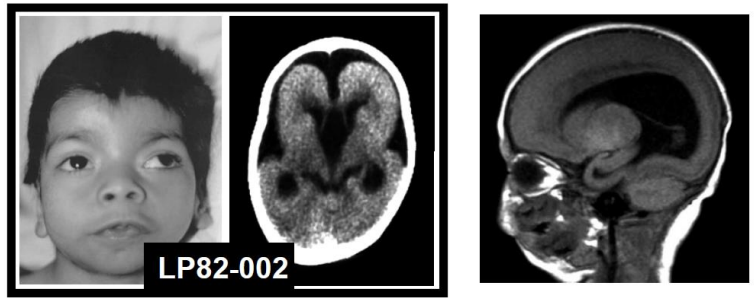
Isolated Lissencephaly Sequence



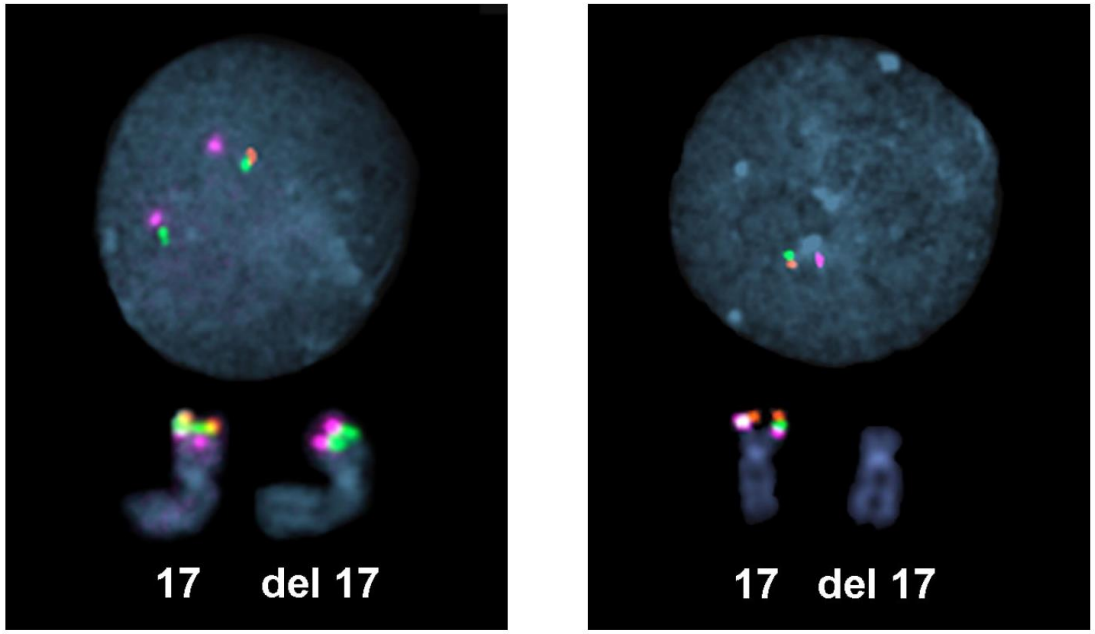
Isolated Lissencephaly Sequence



Miller-Dieker Syndrome



Heterozygous Deletions of 17p13.3 in ILS and MDS



Programmed Cell Death During Development

Brain

Immune System

Limb

Developmental Pathways and Mechanisms

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Developmental Pathways
Evolutionary Conservation of Mechanisms and Pathways

Evolutionary Conservation of Mechanisms and Pathways

Core Pathways

EGF/TGFalpha/EGFR Pathway (via RAS)

Ephrin/Eph Signaling

FGF Signaling

Sonic Hedgehog Signaling

HGF/Met Signaling

NGF Pathway

Notch Signaling

RAS Pathway

TGF-Beta/BMP/Activin Pathway

TNF Signaling

Wnt Signaling

Evolutionary Conservation of Mechanisms and Pathways

Cell Cycle, Proliferation, Apoptosis

Activation of cAMP-Dependent Kinase
Akt Signaling
ATM/BRCA DNA Damage Response/Checkpoint
Apoptosis: Caspase and FAS pathways
Cyclins and Cell Cycle Regulation
EGF/TGFalpha/EGFR Pathway
ERK/MAPK Signaling
Integrin Signaling Pathways
FGF Signaling
Glucocorticoid/Estrogen/Androgen Nuclear Hormone Receptor
GPCR Signaling
Growth Hormone Signaling
Insulin Receptor Signaling
PI3 Kinase/IP3/PTEN Pathway
JAK/STAT Pathway
JNK Pathway
mTOR Pathway
Mismatch Repair
NF-KappaB Pathway

Evolutionary Conservation of Mechanisms and Pathways

Processes

CELL ADHESION

Ephrin/Eph Signaling

Integrin Signaling Pathways

MISCELLANEOUS

HIF1alpha Pathway

Planar Cell Polarity Pathway

Apical Junctional Complex/Polarity Proteins

VEGF Pathway

NGF Pathway

Rho/RhoA GTPase

GDNF Pathway

Endothelin Pathway

Microtubule Motors, Cilia, and Cytoskeleton Vesicle-Mediated Trafficking and Endocytosis Extracellular Matrix Guidance Molecules Junctions, Transporters and Channels

Evolutionary Conservation of Mechanisms and Pathways

General

Chromatin Remodeling

DNA Methylation and Transcriptional Repression

Glucocorticoid/Estrogen/Androgen Nuclear Hormone Receptor Superfamily

Transcription Factor Families (Homeobox, Paired-box, Forkhead, T-box, SOX)

Other Transcription Factors

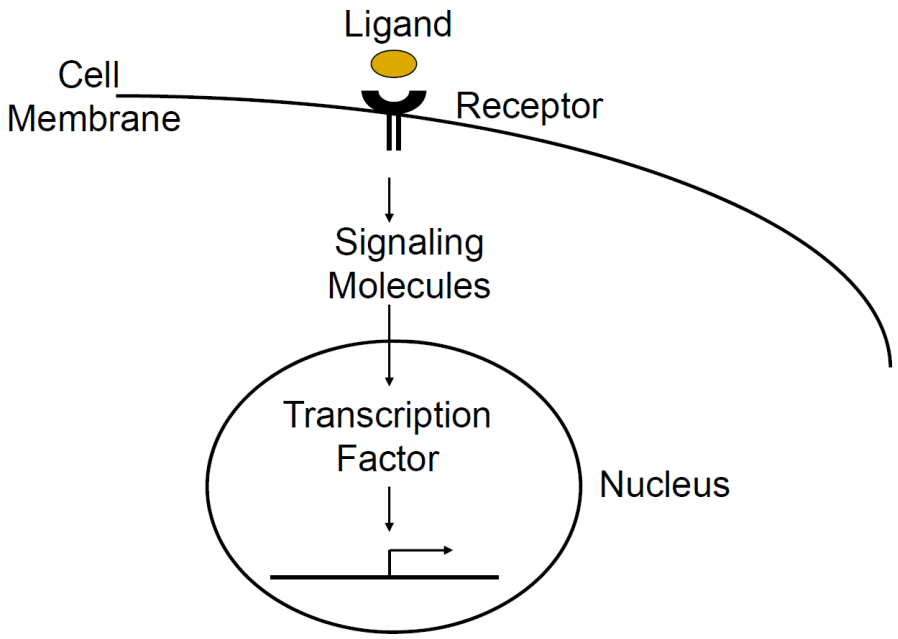
Translational Regulation

Regulation of SUMOylation

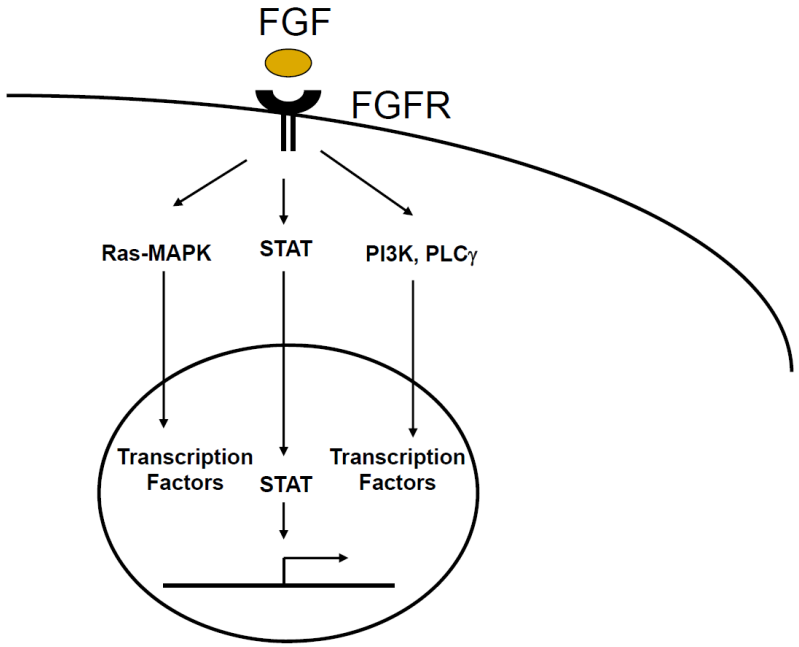
Regulation of Ubiquitination

RNAi Processing Pathway

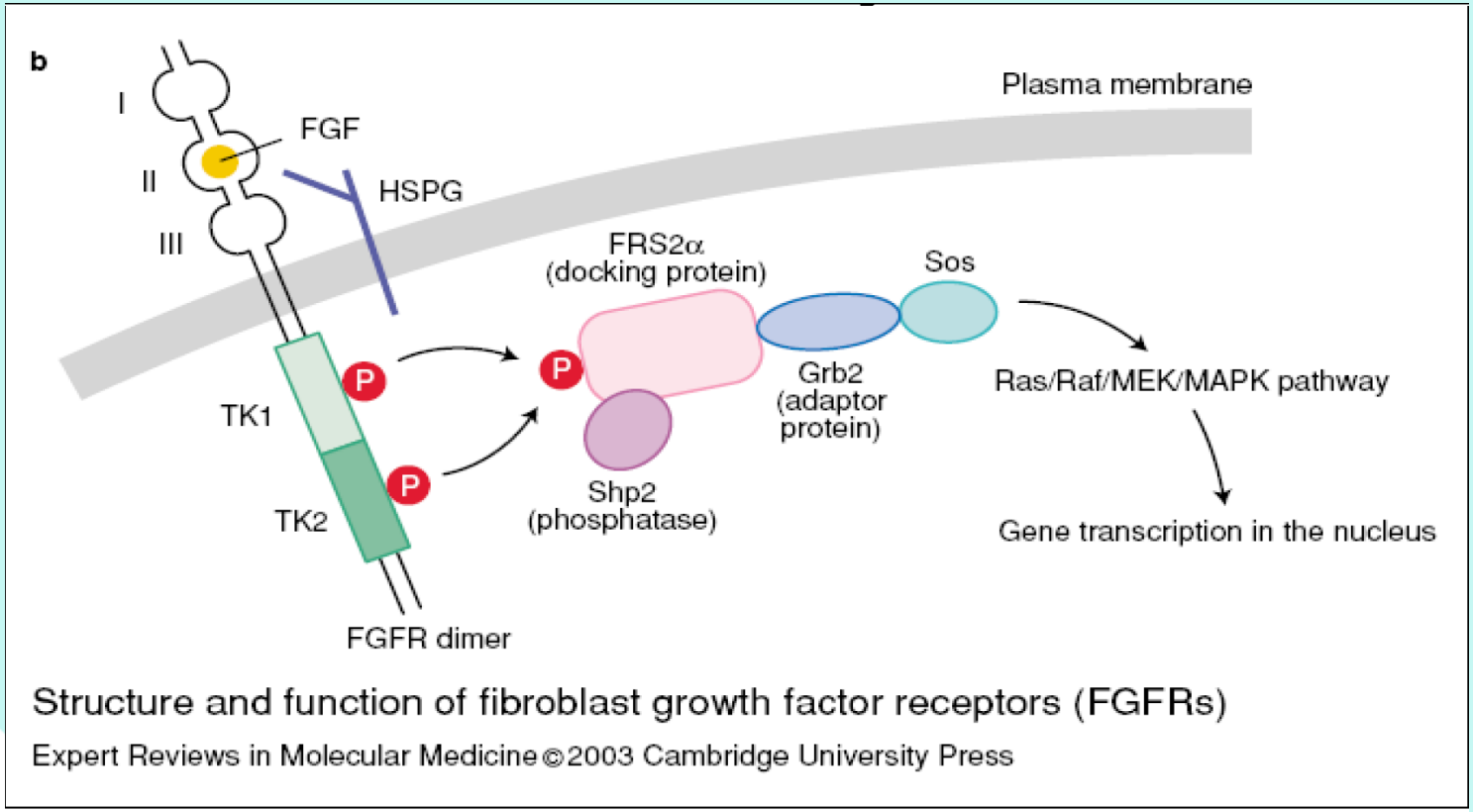
Signal Transduction Pathway



Fibroblast Growth Factor Signaling



Fibroblast Growth Factor Pathway

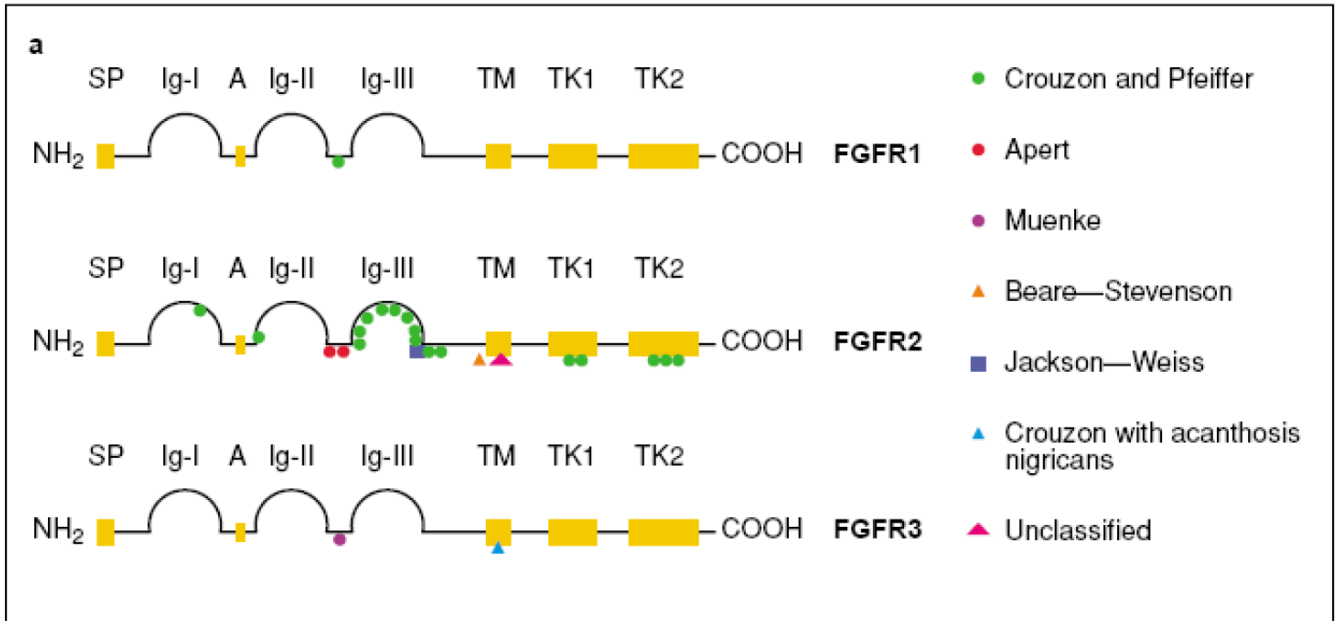


Structure and function of fibroblast growth factor receptors (FGFRs)

Expert Reviews in Molecular Medicine ©2003 Cambridge University Press

Bonaventure and El Ghouzzi. Expert Rev Mol Med 2003:1-17, 2003

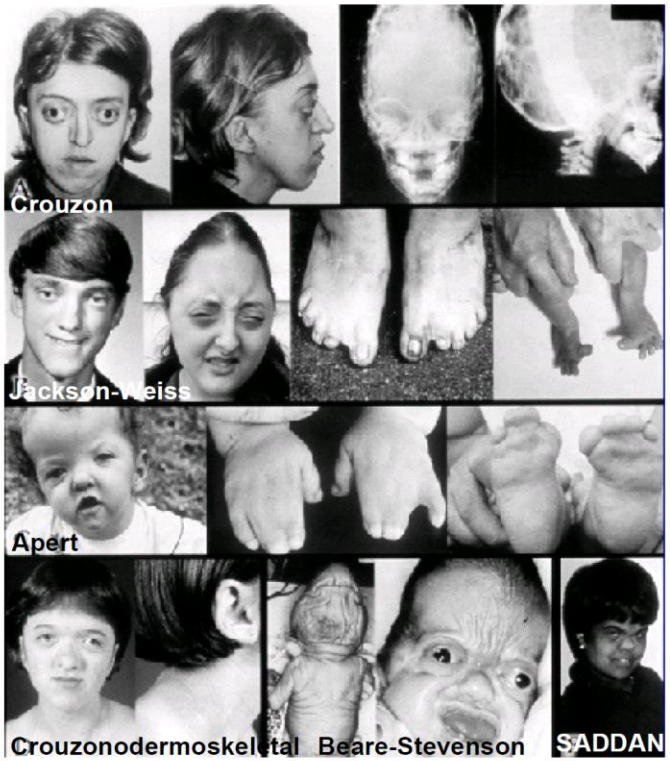
Fibroblast Growth Factor Receptors



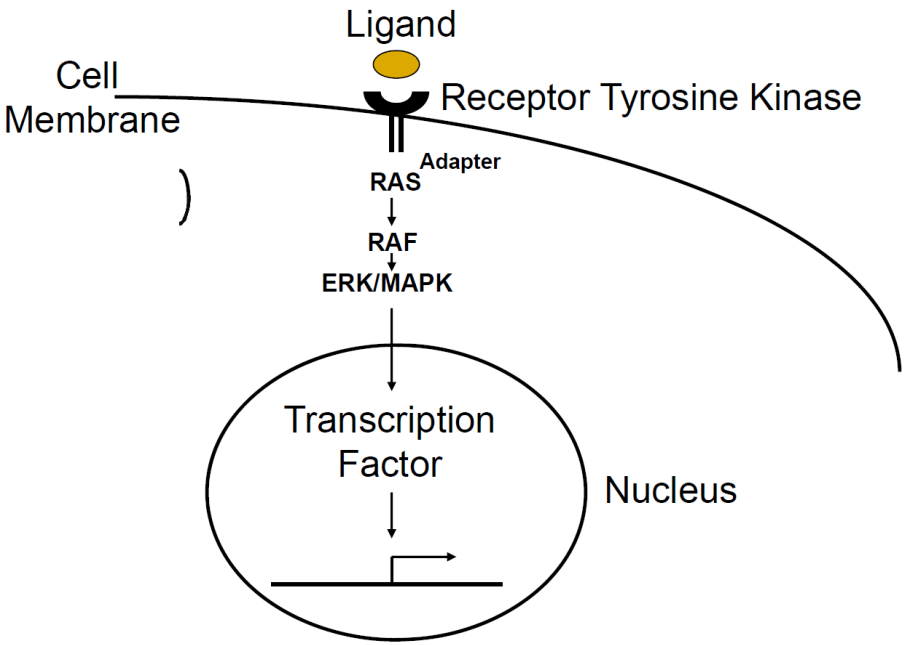
Bonaventure and El Ghouzzi. Expert Rev Mol Med 2003:1-17, 2003

FGFR Craniosynostosis Syndromes

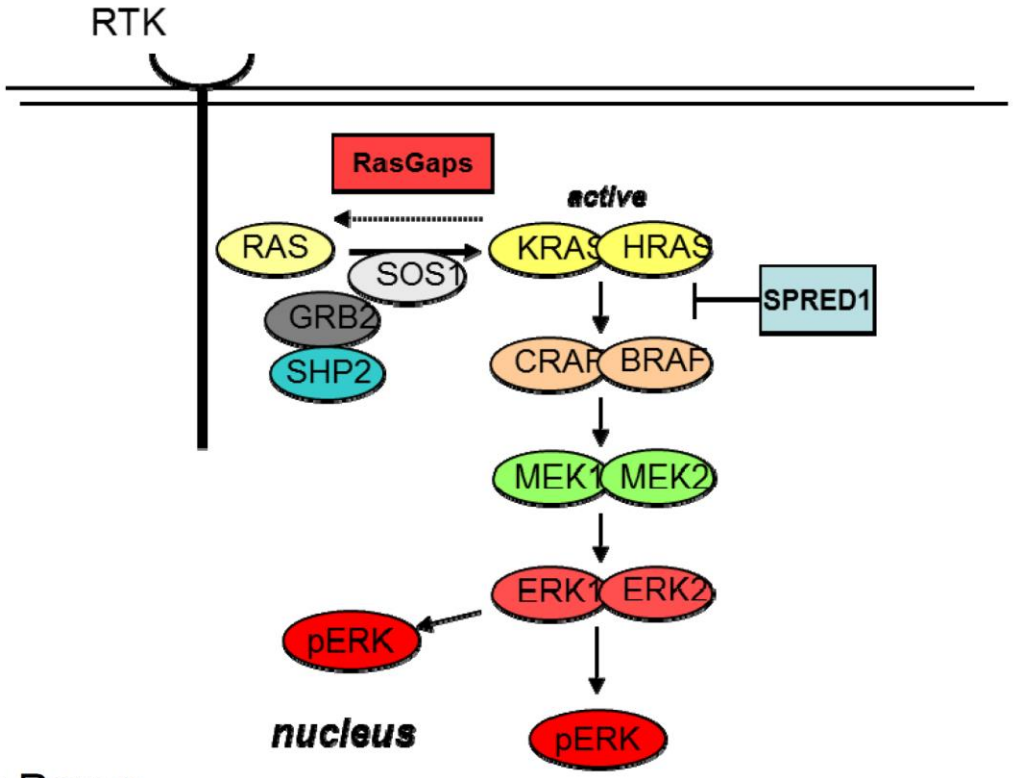
- Autosomal dominant
- Genetic heterogeneity
- Phenotypic variability
- Gain of function mutations, missense and in-frame deletions and insertions, splice-site mutations in 85 to 90%



Jabs. ed. Jameson, Principles of Molecular Medicine, 1998

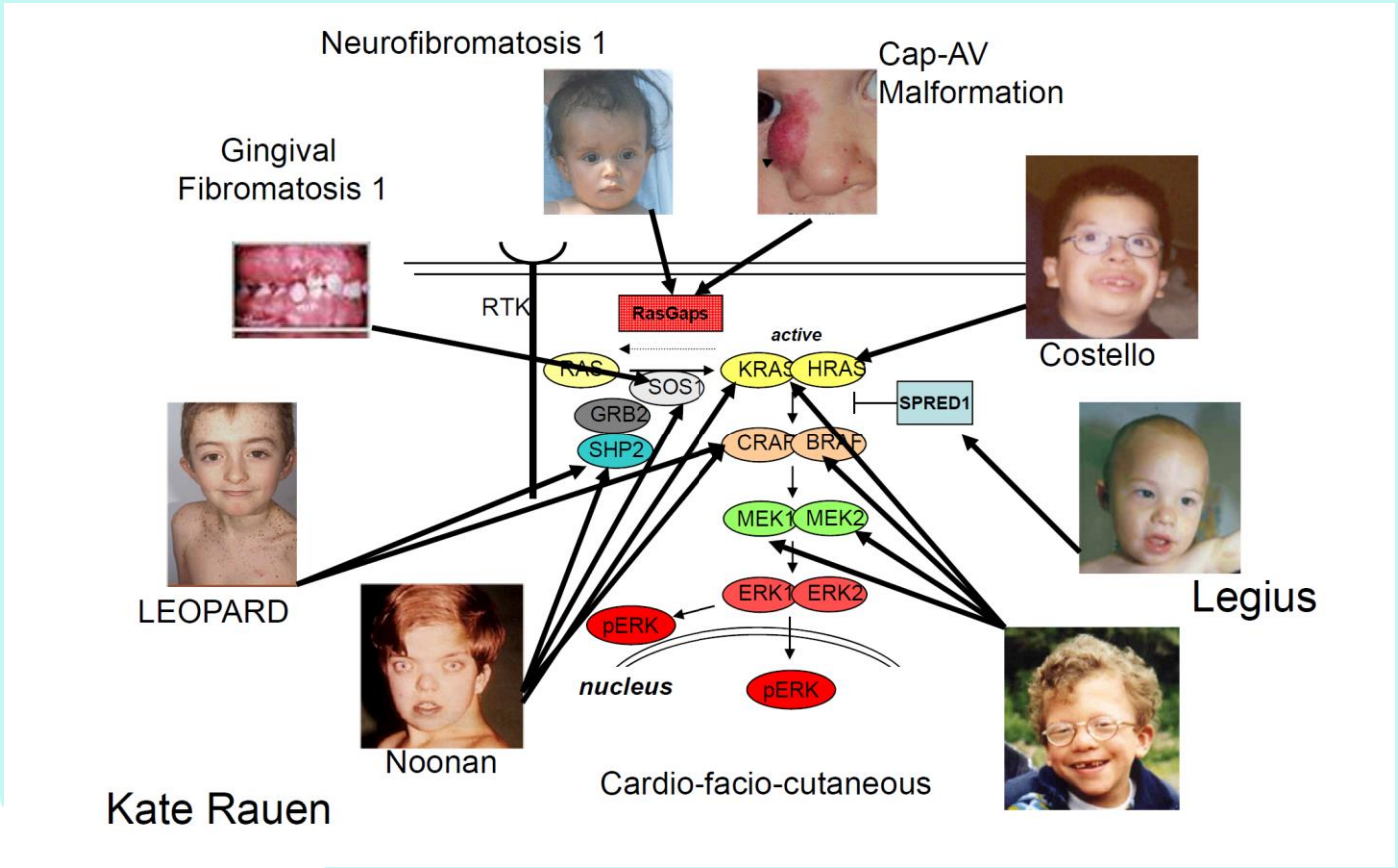

Ligand
Cell
Membrane
Receptor Tyrosine Kinase
Adapter
RAS
RAF
ERK/MAPK
Transcription
Factor
Nucleus

RAS/MAPK Pathway



Kate Rauen

Genetic Syndromes of the RAS/MAPK Pathway



THE END
THANK YOU!

Developmental Genetics