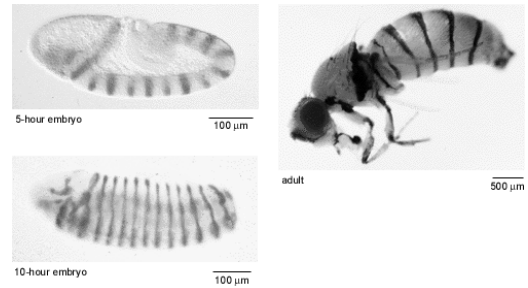


Hedgehog pathway

- First described in *Drosophila*
- Conserved signal transduction cascade
- Highly relevant to human development, disease, cancer, stem cell biology
- Important cell biology, gene regulation questions
- Therapeutic target, especially cancer

Embryonic patterning-early establishment of the body plan

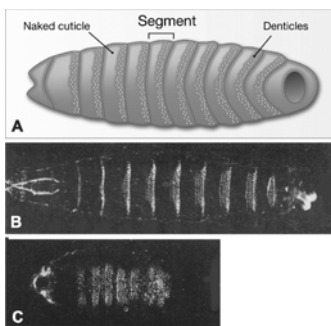
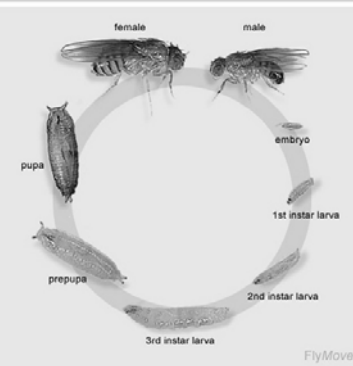


The Nobel Prize in Physiology or Medicine 1995

Edward B. Lewis, Christiane Nüsslein-Volhard and Eric F. Wieschaus

for their discoveries concerning
"the genetic control of early embryonic development".

The life cycle of *Drosophila melanogaster*

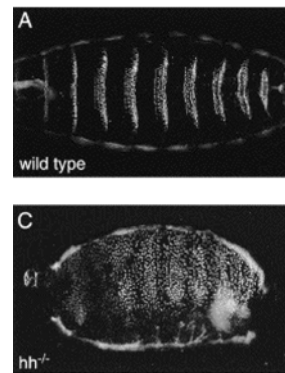


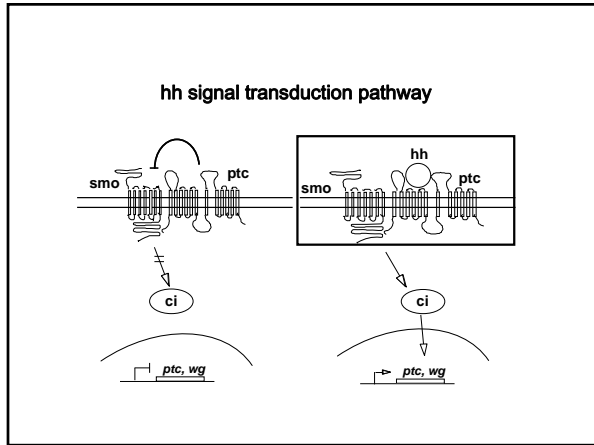
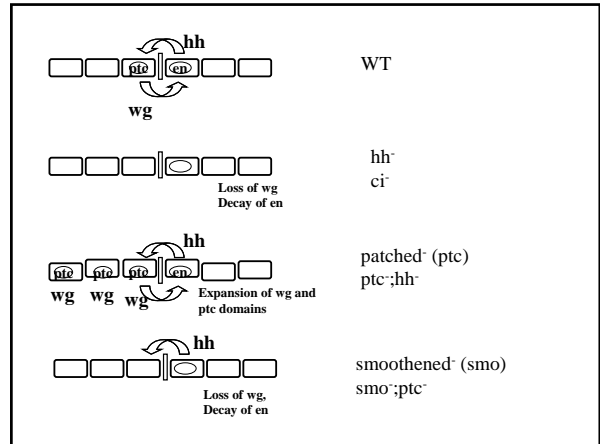
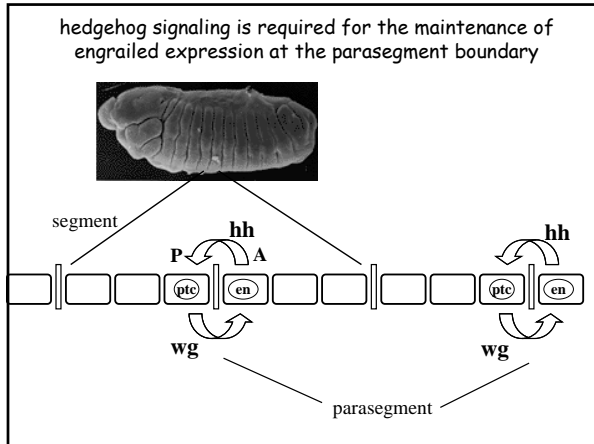
van den Brink G R Physiol Rev 2007;87:1343-1375

Physiological Reviews

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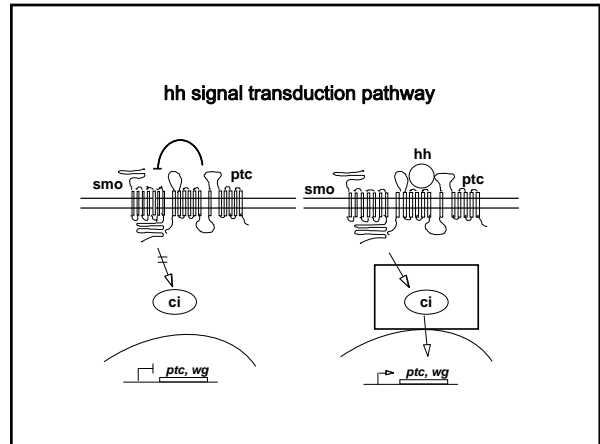
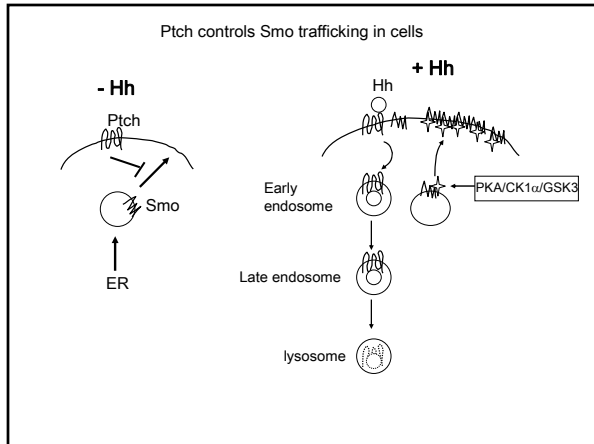
How did the hedgehog gene get its name?

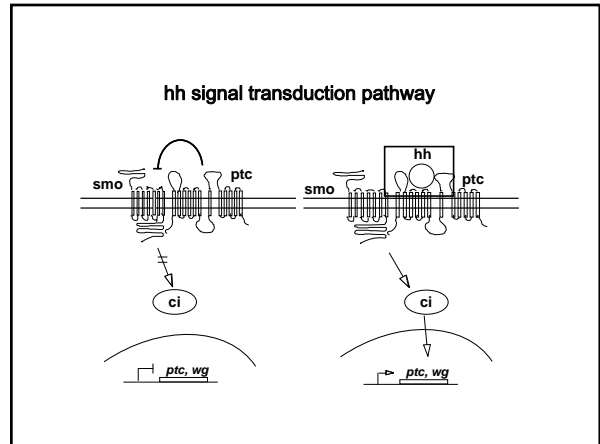
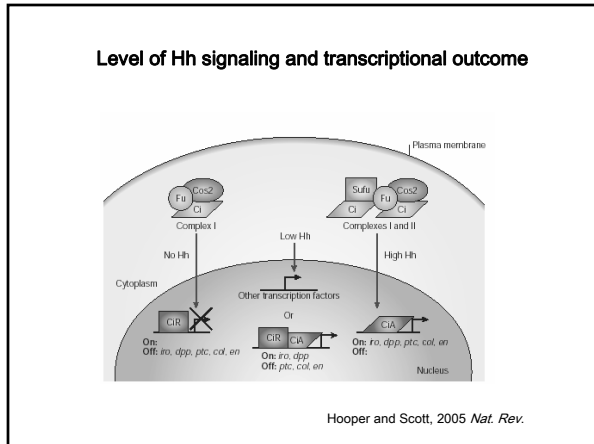
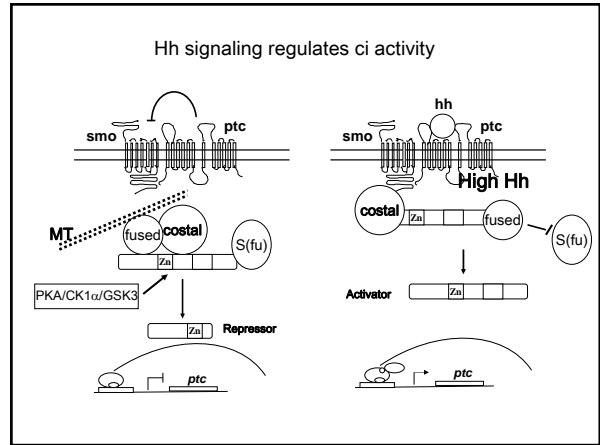
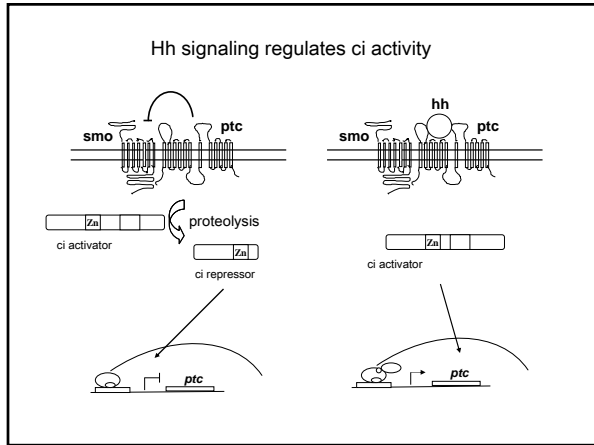
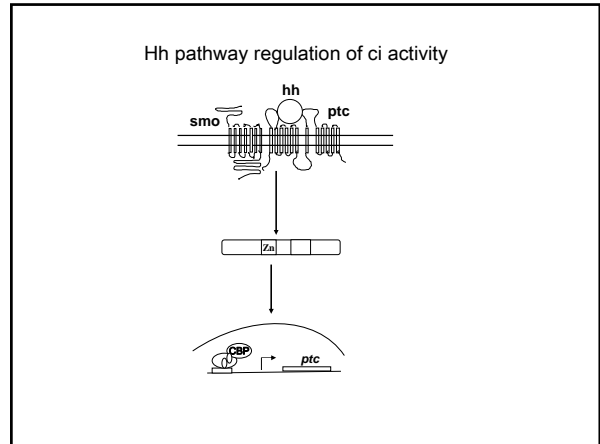
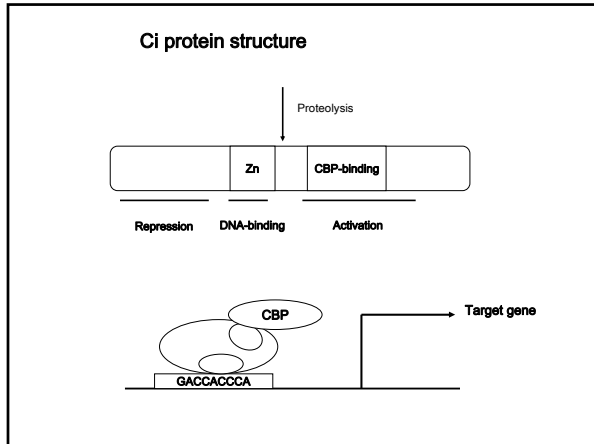




Activation of the Hh signaling cascade

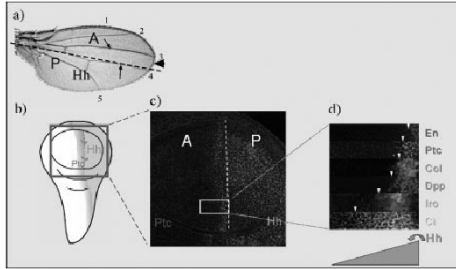
- Ptch and Smo never co-localize
- Ptch negatively regulates the translocation of Smo to the cell surface
- Smo activation requires conformational changes and phosphorylation





Hh signaling mediates long range patterning in the fly wing

Cells adopt different fates in response to different concentrations of Hh



NH2 [signaling] [catalytic] COOH

signaling catalytic

Hh-N Hh-C

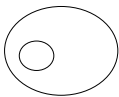
Rescue hh flies No rescue

Localization and secretion of the Hh protein is depends on the carboxy terminus

Localization of the protein

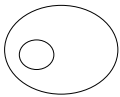
Hh full length

Intracellular cell surface secreted



+++ +++ +/-

Hh-N



+ + +++++

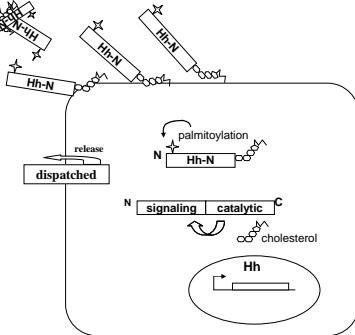
Transgenic rescue of hh mutant flies
Patterning changes elicited by FL versus NH2-terminal hh constructs

Full length Hh

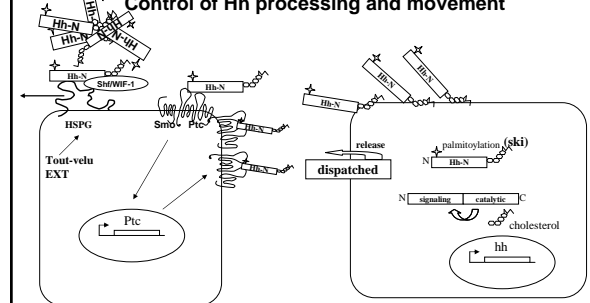
Hh-N



Hh posttranslational modifications



Control of Hh processing and movement



Hh pathway-conservation in vertebrate species

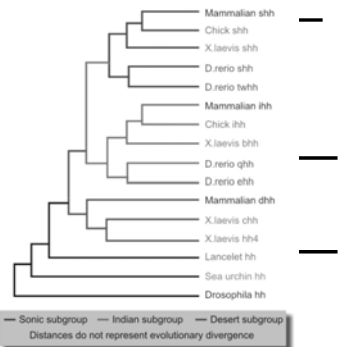


Table 1 | A comparison of the Hedgehog pathway in *Drosophila melanogaster* and mammals

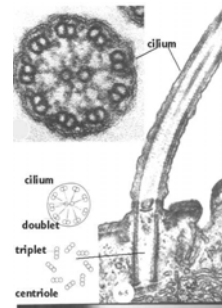
	<i>D. melanogaster</i>	Mammals
Ligands	Hh	SHH, DHH, IHH
Acyl transferase	Rasp	SKH
Mutase	Disp	DISPA
Receptors	Ptc	PTC1, PTC2
Glycan	Dlp	?
Other Hh-binding factors	Sfr, Puh?	HIP, GAS1, moogalin
Initiator	Smo	SMO
Smo-regulators	PKA, Cki, CSK3b	h-hedgehog-2, GRK2
Cytoplasmic regulators	Cos2	KIF7, KIAA39, JET88, JET172, Rab23, NMM/REG4, FRPBB, SU
	Fu, Sufu	FU(7), SUFU, Iguana
Transcription factors	Ci	GLI1, GLI2 and GLI3

Hooper and Scott, 2005 *Nat. Rev.*

Divergence of fly and vertebrate signaling pathways

- Smoothened regulation
- Ci/Gli regulation

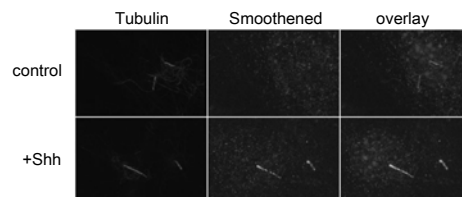
Hedgehog and the primary cilium

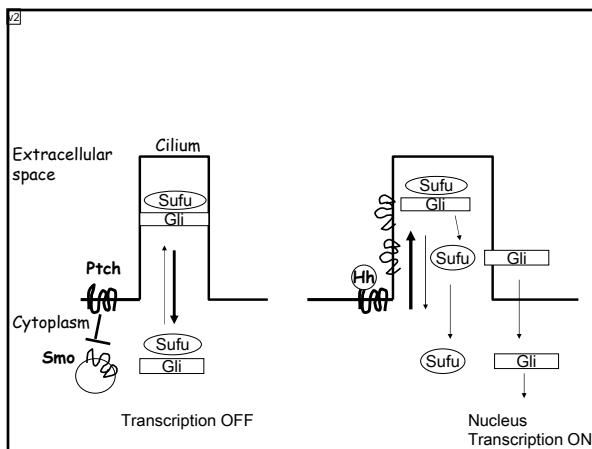
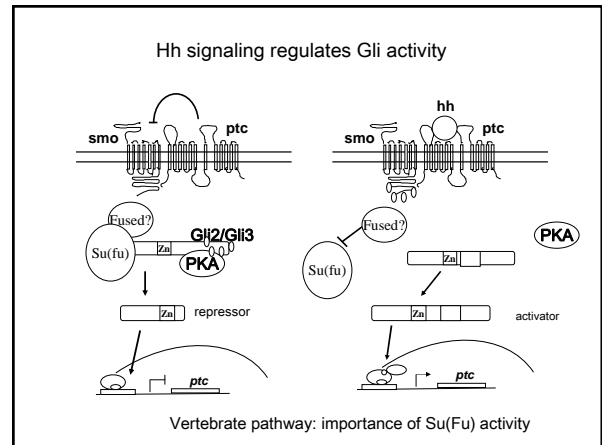
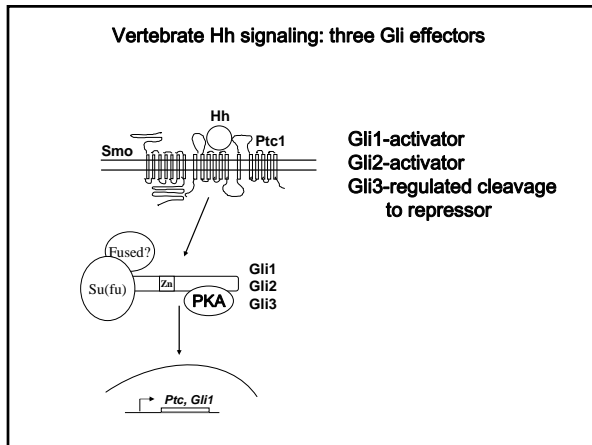
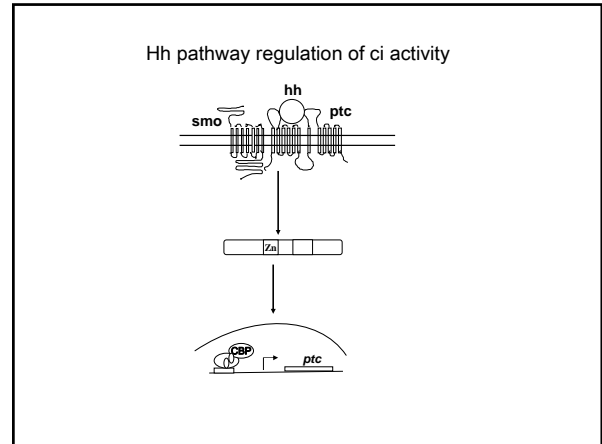
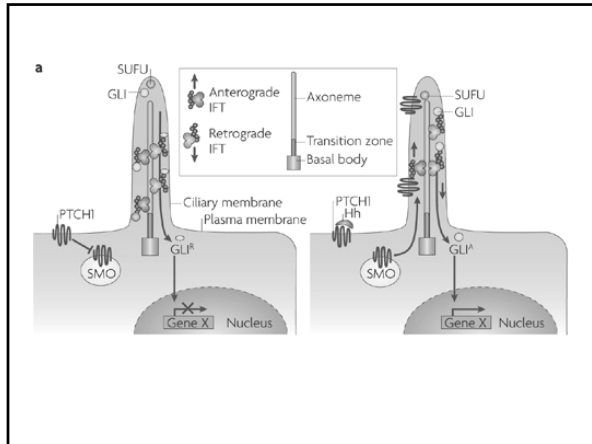


Cilia are required for Hh signaling

- Mutations in structural components of the cilia resemble loss of function for Hh signaling
- Intact cilia are required for Gli processing
- Ptc controls Smo entry into the cilium

Hedgehog induces the accumulation of Smo to the cilium





Conservation of the Hh pathway components and function in vertebrates

Mammalian Hh homologues

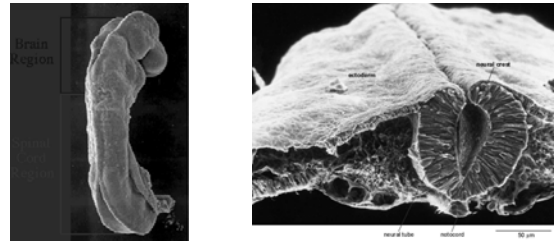
- Dhh: testes, peripheral nerve sheath
- Ihh: chondrocyte development, gut, cardiac morphogenesis, kidney development, placentation
- Shh: neural tube patterning, muscle, proliferation, left-right asymmetry, limb polarity, epithelial-mesenchymal interactions (gut, lung) stem cell maintenance

Functional conservation in patterning
Vertebrate and *Drosophila* eye and limb

Genetic evidence for the requirement for Hh signaling components in vertebrates

- Shh
- Smo
- Ptc
- Dispatched
- Gli

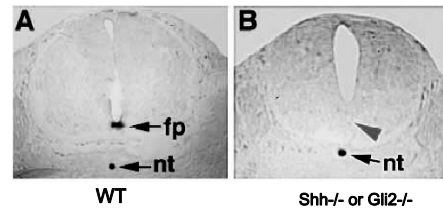
Shh and dorsal-ventral patterning in the CNS



Shh is the notochord-derived signal that induces the floor plate

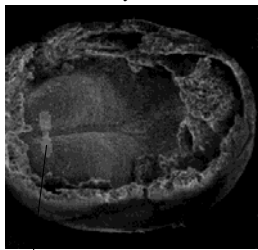


Genetic evidence for the requirement for hh signaling components in vertebrates



Shh and Gli2 are required for specification of the CNS ventral midline

Day 17

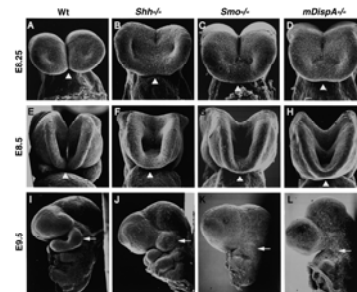


Early eye field

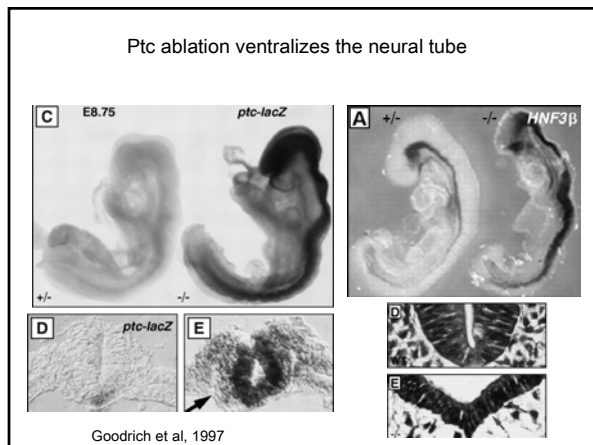
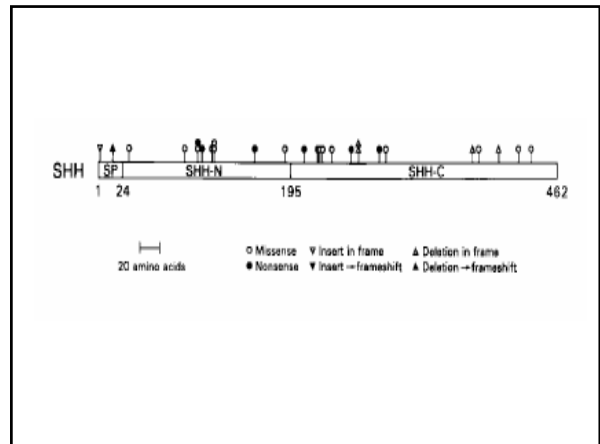
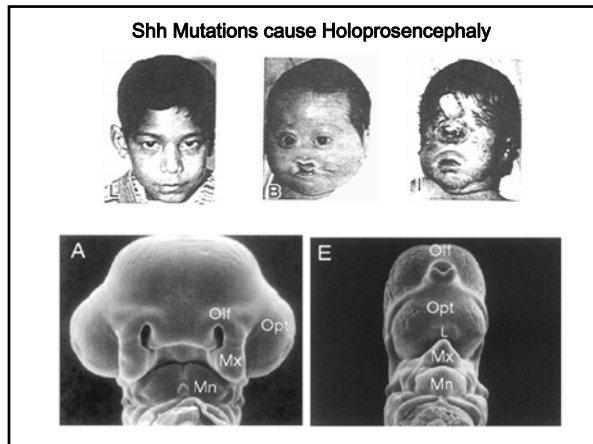
Day 21



Eye field pushed forward



Smo and mDispA also required for midline specification



Genetic disease-types of inheritance

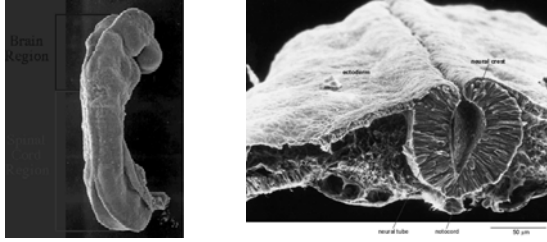
Inheritance pattern	Description	Examples
<u>Autosomal dominant</u>	Only one mutated copy of the gene is needed for a person to be affected by an autosomal dominant disorder.	Huntingtons disease, Neurofibromatosis I, Marfan Syndrome, Hereditary nonpolyposis colorectal cancer, Hereditary multiple exostoses
<u>Autosomal recessive</u>	Two copies of the gene must be mutated for a person to be affected by an autosomal recessive disorder.	Cystic fibrosis, Sickle cell anemia, Tay-Sachs disease, Spinal muscular atrophy
<u>X-linked dominant</u>	X-linked dominant disorders are caused by mutations in genes on the X chromosome. Females are more frequently affected than males, and the chance of passing on an X-linked dominant disorder differs between men and women.	Hypophosphatemia, Aicardi Syndrome

<u>X-linked recessive</u>	X-linked recessive disorders are also caused by mutations in genes on the X chromosome. Males are more frequently affected than females, and the chance of passing on the disorder differs between men and women.	Hemophilia A, Duchenne muscular dystrophy, Color blindness, Muscular dystrophy, Androgenetic alopecia
<u>Y-linked</u>	Y-linked disorders are caused by mutations on the Y chromosome. Only males can get them, and all of the sons of an affected father are affected.	Male Infertility
<u>Mitochondria</u>	This type of inheritance, also known as maternal inheritance, applies to genes in mitochondrial DNA. Because only egg cells contribute mitochondria to the developing embryo, only females can pass on mitochondrial conditions to their children.	Leber's Hereditary Optic Neuropathy (LHON)

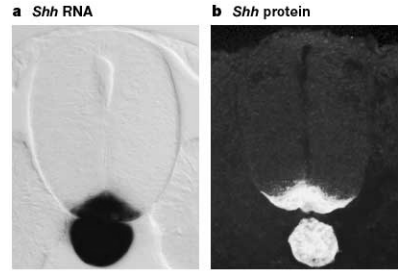
Hedgehog pathway genes associated with Congenital defects in humans

Condition	Gene	Phenotype
Holoprosencephaly	Shh Haploinsufficiency	Midline defects
Smith-Lemli-Opitz	Cholesterol biosynthesis	Midline defects
Gorlin Syndrome	Ptc Haploinsufficiency	Multiple developmental defects, tumours
Greig's cephalopolysyndactyly	Gli3 Haploinsufficiency	Limb malformations and other defects
Pallister-Hall syndrome	Gli3 Haploinsufficiency	Limb malformations and other defects
Postaxial polydactyly	Gli3 Haploinsufficiency	Ectopic postaxial digit

Shh and dorsal-ventral patterning in the CNS



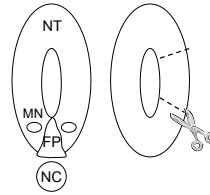
Shh is the notochord-derived signal that induces the floor plate



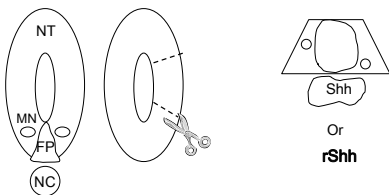
Floor plate and motorneuron induction by Sonic hedgehog



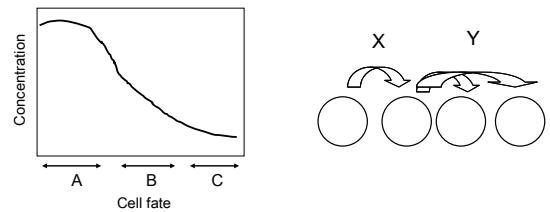
Floor plate and motorneuron induction by Sonic hedgehog

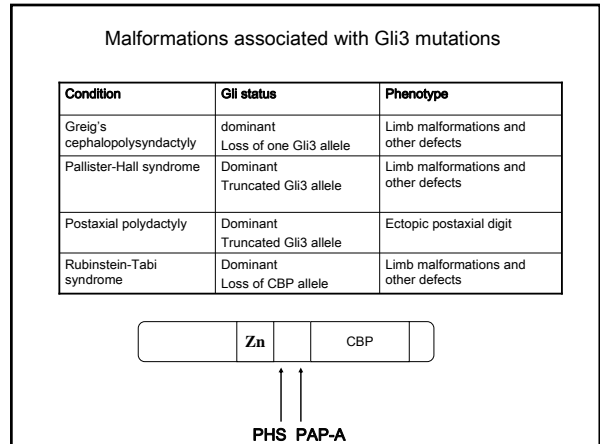
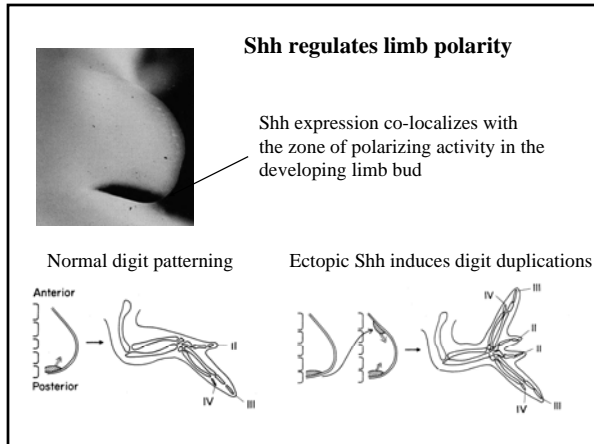
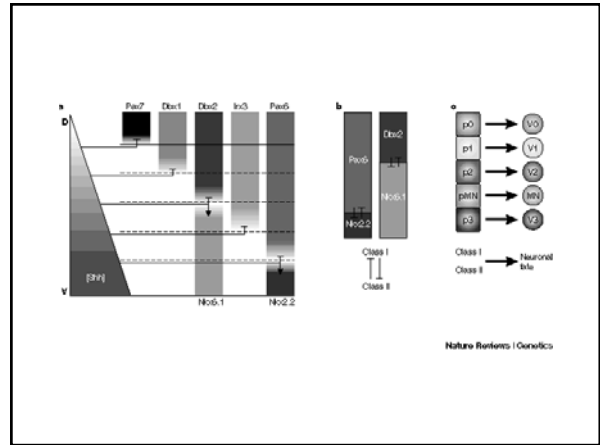
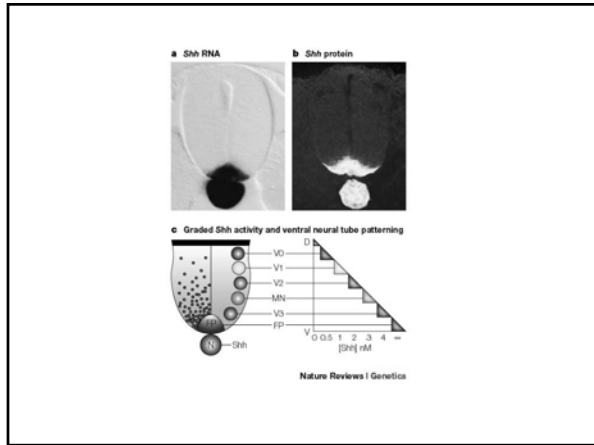
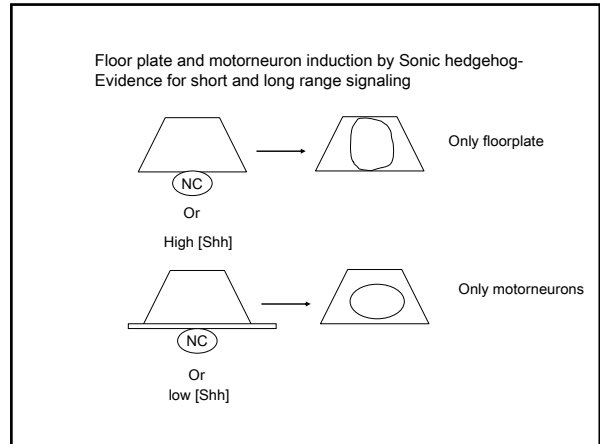
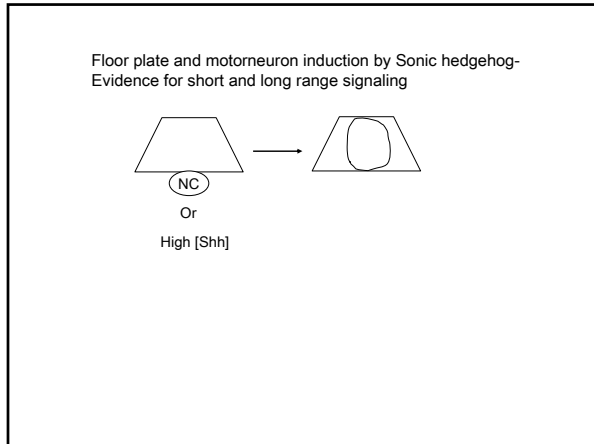


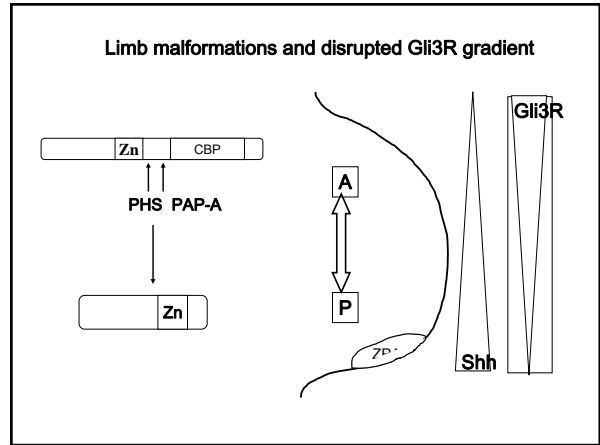
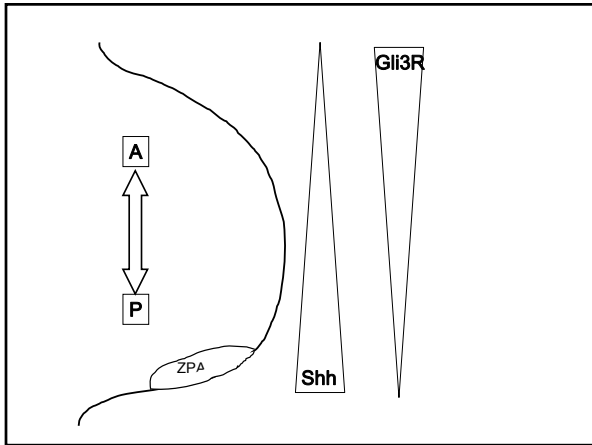
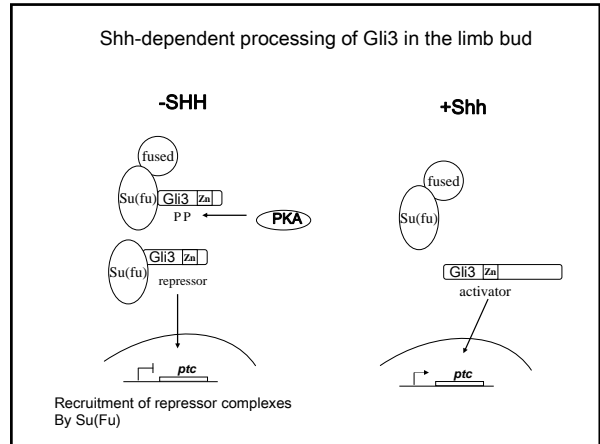
Floor plate and motorneuron induction by Sonic hedgehog



Morphogen versus second signal hypothesis







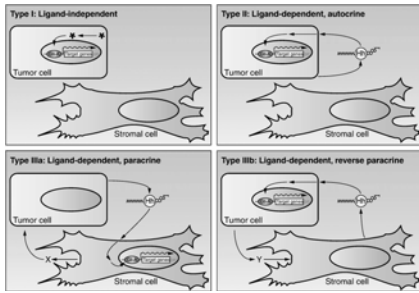
Shh/proliferation and cancer

- Cerebellum
- Retina
- Sclerotome
- Lung
- Muscle
- GI tract
- Hair follicle

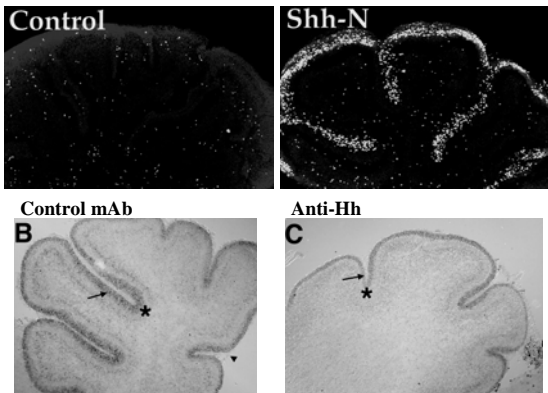
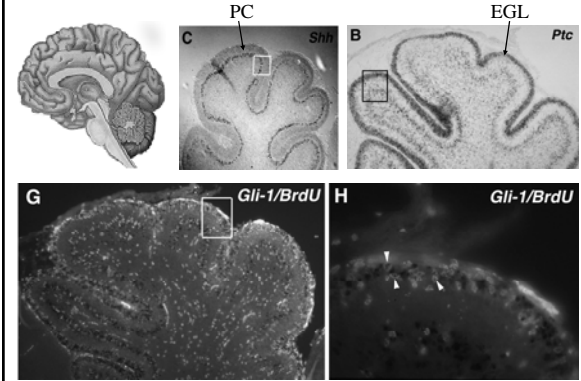
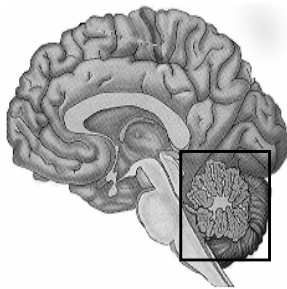
The Hh pathway and tumorigenesis

Tumour	Gene	Mutation
Basal cell carcinoma	Ptc1	Inactivating
Medulloblastoma	Su(Fu)	Inactivating
Rhadomyosarcoma	Smo	Activating
	Gli1	Ectopic expression/amplification
Glioblastoma	Gli	Amplification
Osteosarcoma	Gli1	Amplification
B-cell lymphoma	Gli1	Amplification
Pancreas, stomach, lung, prostate	LIGAND DRIVEN	

Hh associated tumorigenesis



Hedgehog signaling and proliferation and cancer in the brain



Blocking Hh signaling blocks proliferation in the Developing cerebellum

