Human Development:

Fertilization through gastrulation

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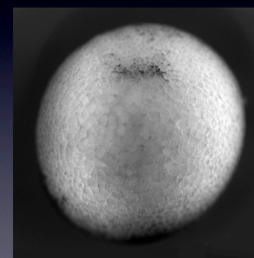
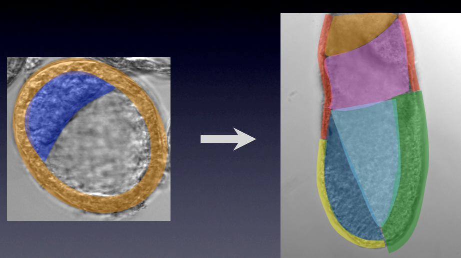
Gastrulation movements in the frog embryo

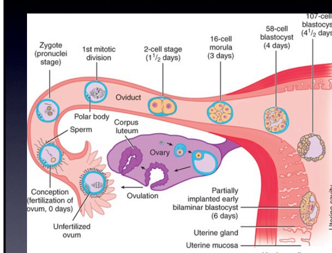


Vegetal view

From blastula to gastrula

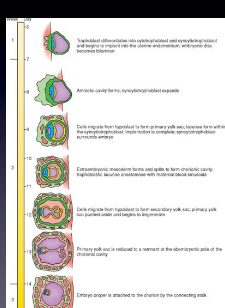


The first week of development



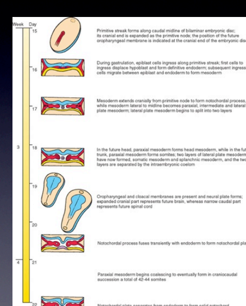
- Fertilization
- Cleavage stages
- Blastocyst formation
- Early lineage specification
- Implantation

The second week of development



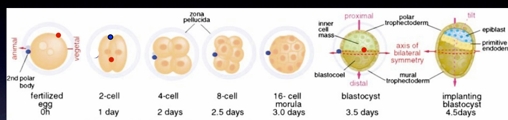
- Trophoblast differentiation
- Yolk sac formation
- Anterior-posterior axis patterning
- Initiation of gastrulation

The third week of development



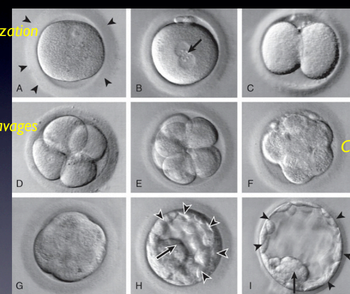
- Endoderm and mesoderm ingression
- Mesoderm lineage specification
- Left-right patterning
- Neural plate formation
- Axial midline formation

Pre-implantation mouse development

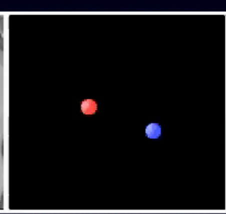


- Reductive cleavage
- Blastomere potency
- Inside-outside allocation of lineage progenitors
- Compaction
- Blastocyst formation
- Emerging morphological asymmetry

Human embryo development in culture



Early cleavages of the mouse embryo



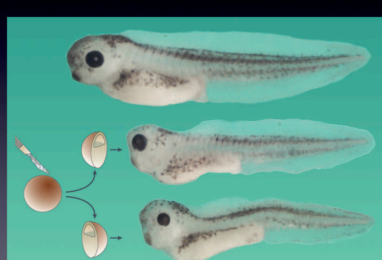
(Bischoff et al. (2008))

Key properties of vertebrate embryogenesis

- Regulative development

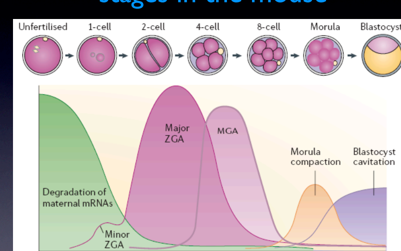
Early blastomeres are totipotent

Regulative development of the vertebrate embryo



(DeRobertis (2006))

Gene expression at pre-implantation stages in the mouse

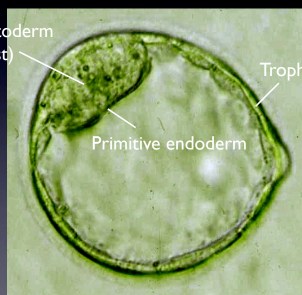


Zygotic genome activity

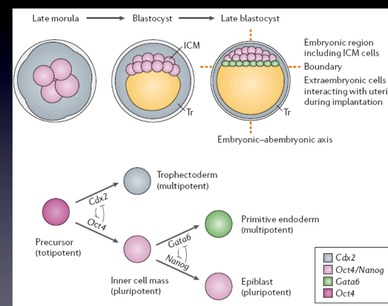
Mid-preimplantation genome activity

(Wang and Dey (2006))

Cell types of the blastocyst

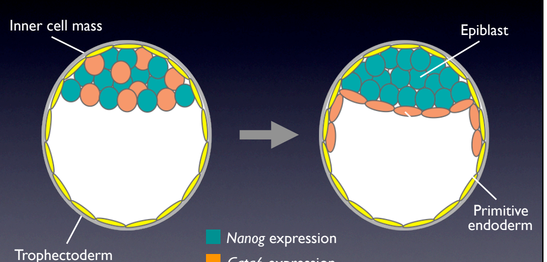


Specification of early lineages



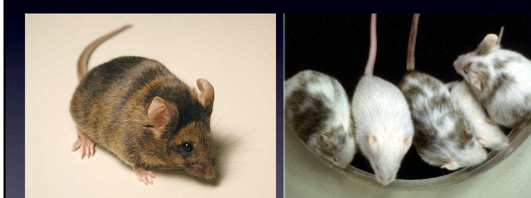
(Wang and Dey (2006))

Model for primitive endoderm (hypoblast) specification



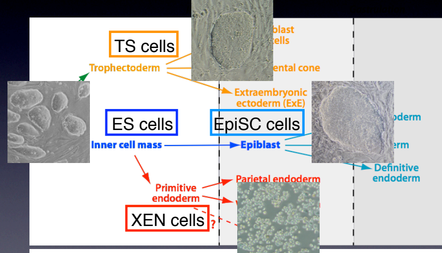
(Chazaud *et al.* (2006))

Pluripotency of mouse ES cells



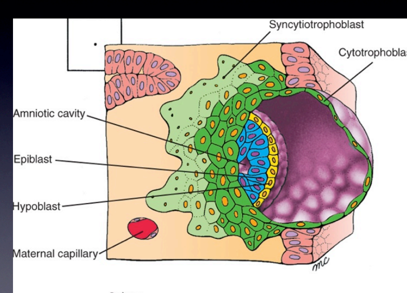
Can contribute to all embryonic cell types in chimeras – including the germ line

Early lineages and stem cells in the mouse embryo

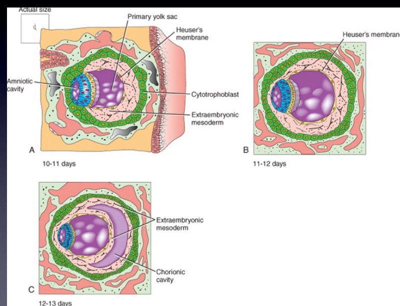


Mouse EpiSC cells resemble human ES cells

Process of implantation



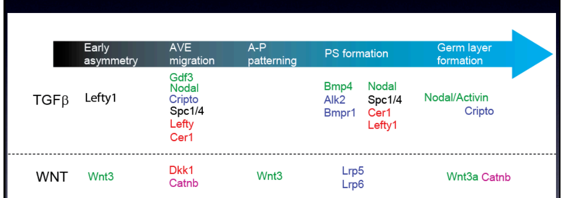
Formation of extraembryonic tissues



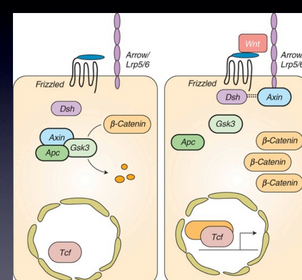
Key properties of vertebrate embryogenesis

- Regulative development
- Patterning at a distance by soluble morphogens

Two major signaling pathways regulate early patterning and differentation

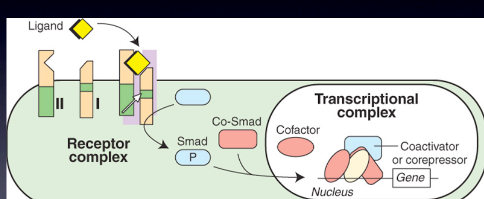


Schematic pathway for canonical Wnt/ beta-catenin signaling

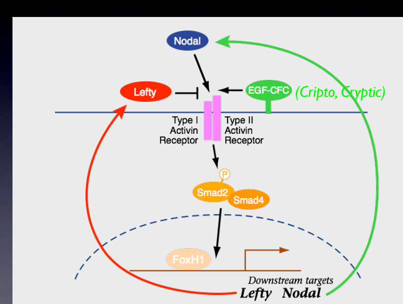


Wnt ligand absent Wnt ligand present

Schematic pathway for TGF-beta signaling



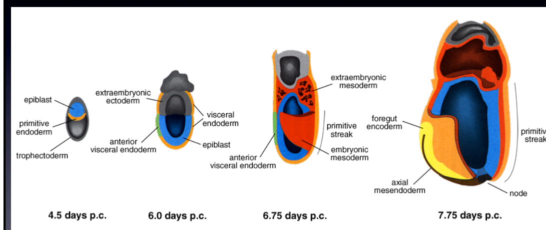
The Nodal signaling pathway



Key properties of vertebrate embryogenesis

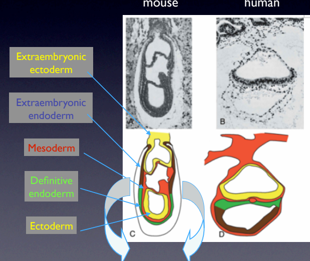
- Regulative development
- Patterning at a distance by soluble morphogens
- Common patterning mechanisms underlie distinct embryo morphologies

Schematic of early mouse development



(Adapted from Hogan *et al.* (1994))

Morphological relationship between mouse and human embryos

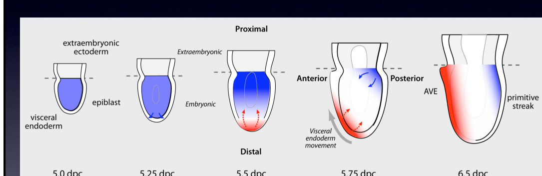


(Eakin and Behringer)

Key properties of vertebrate embryogenesis

- Regulative development
- Patterning at a distance by soluble morphogens
- Common patterning mechanisms underlie distinct embryo morphologies
- Antagonism of secreted ligands and inhibitors

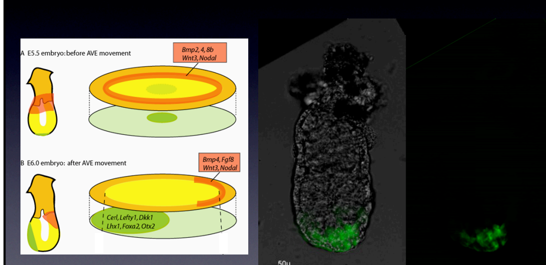
Specification of the anterior-posterior axis in the mouse



Nodal and Cripto activity

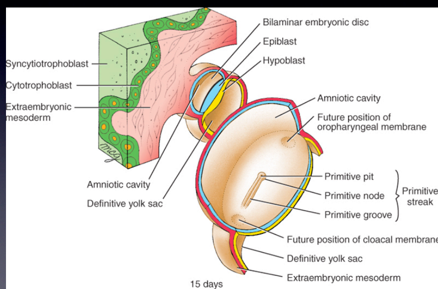
Nodal inhibitor activity (Lefty, Cerberus)

Movement of the anterior visceral endoderm

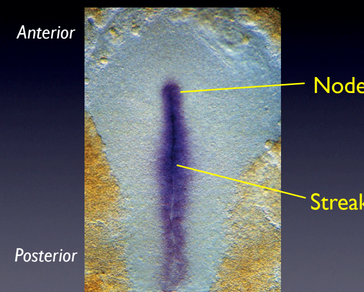


View from anterior side

Relationship of blastodisc to implantation site

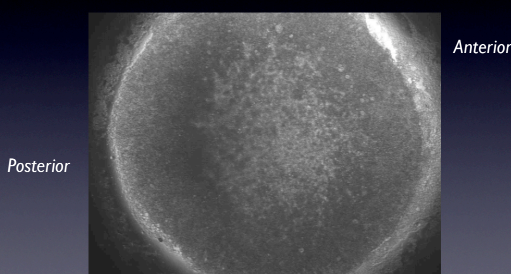


Formation of the primitive streak

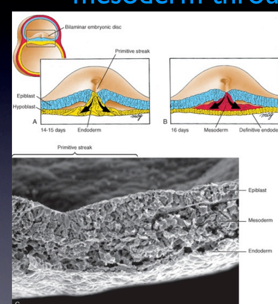


Expression of Brachyury in chick embryo

Early embryogenesis in the chick

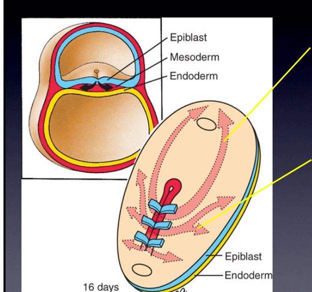


Ingression of nascent endoderm and mesoderm through the streak



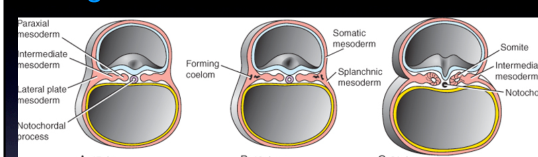
- Delamination of epiblast cells
- Movement through the streak
- Initial ingression of endoderm
- Subsequent ingression of mesoderm

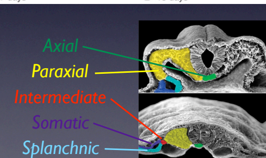
Anterior and lateral migration of mesoderm



- *Anterior migration of mesoderm:*
  - *Axial (prechordal)*
  - *Cardiac*
- *Lateral distance from midline determines mesoderm type:*
  - Axial (e.g., notochord)
  - Paraxial (somites)
  - Intermediate (e.g., kidney)
  - Lateral (e.g, limbs)

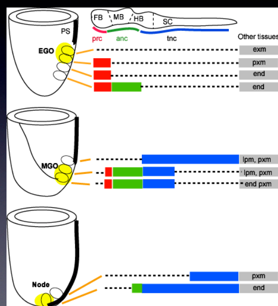
Regional differentiation of mesoderm





Chick embryo

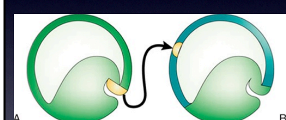
Anterior-posterior patterning of axial mesoderm



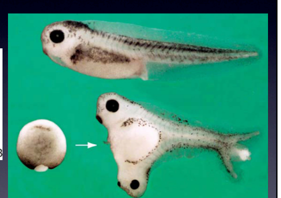
Key properties of vertebrate embryogenesis

- Regulative development
- Patterning at a distance by soluble morphogens
- Common patterning mechanisms underlie distinct embryo morphologies
- Antagonism of secreted ligands and inhibitors
- Instructive inductive interactions

Spemann-Mangold organizer experiment



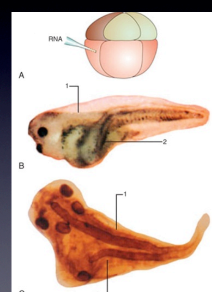
Blastopore lip transplantation



Induction of secondary axis

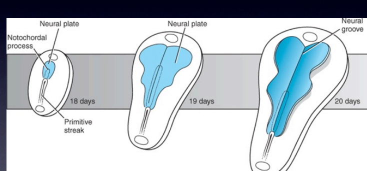
(DeRobertis and Kuroda (2004))

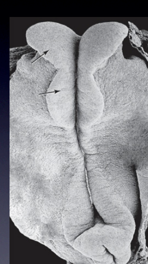
Injection of Wnts or Nodal can induce a secondary axis



- *Injection of mRNA into dorsal marginal zone*
  - Wnt8 (complete axis)
  - Nodal (partial axis)

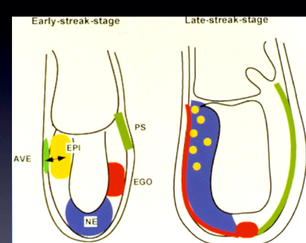
Formation of the neural plate





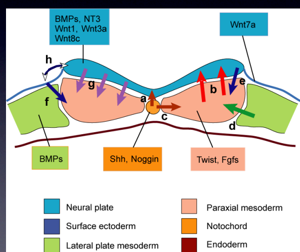
Macaque embryo
(similar to 20 day human embryo)

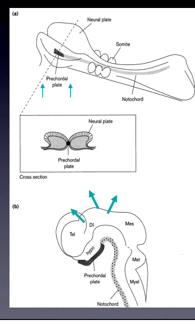
Inductive interactions and head formation



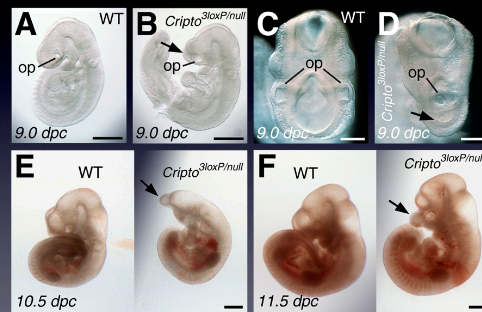
AVE Anterior visceral endoderm
EPI Epiblast
NE Neural progenitor
EGO Early gastrula organizer
PS Primitive streak

Dorsoventral patterning by axial and paraxial mesoderm

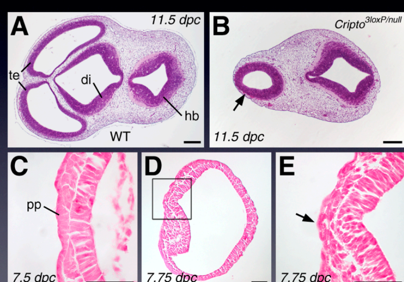




Holoprosencephaly in *Cripto* hypomorphs

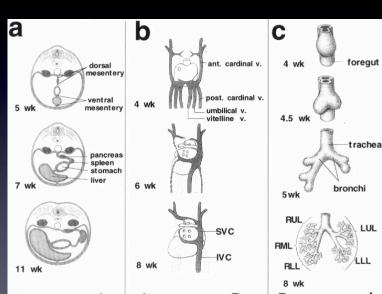


Defective forebrain patterning and axial mesoderm formation



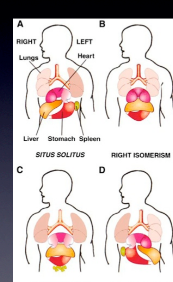
Spectrum of human holoprosencephaly

Complex L-R laterality of tissues



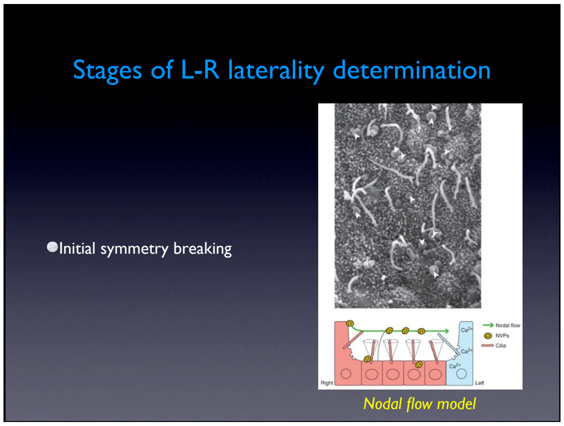
(Kosaki and Casey (1998))

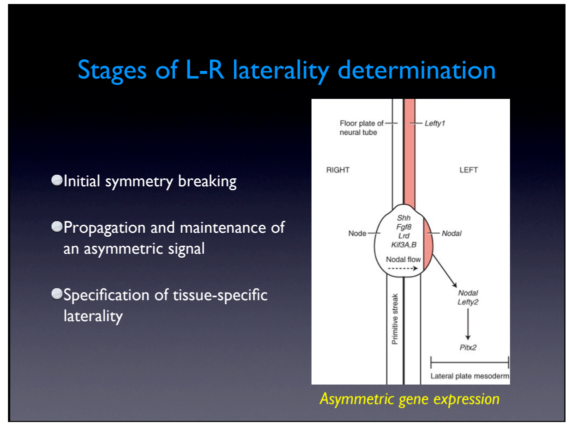
Nomenclature for L-R laterality phenotypes

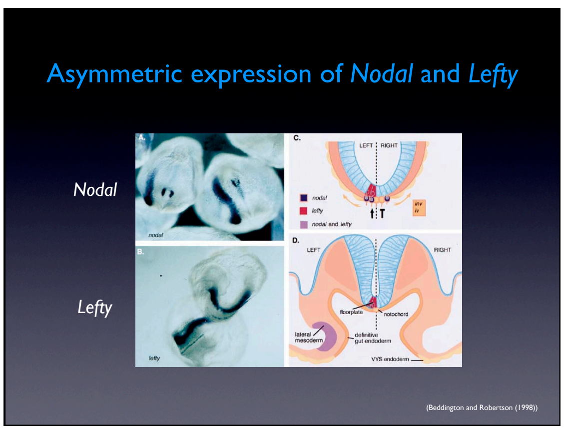


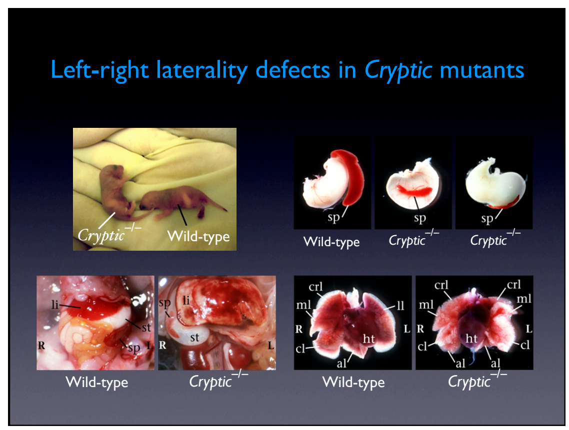
- *Situs solitus:* normal organ position
- *Situs inversus:* complete reversal of organ position
- *Isomerism:* mirror image duplication of tissue morphology
- *Heterotaxia:* discordant and randomized organ position

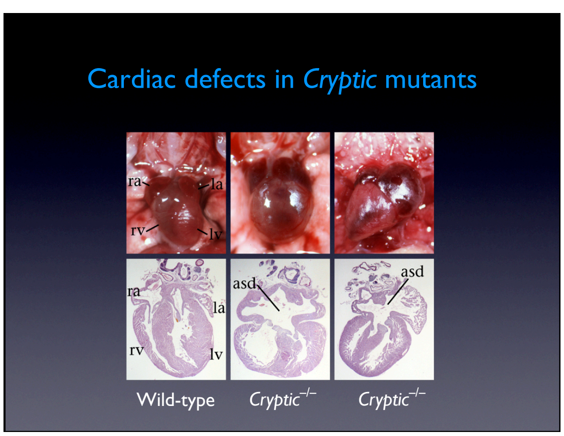
(Capdevila et al. (2000))

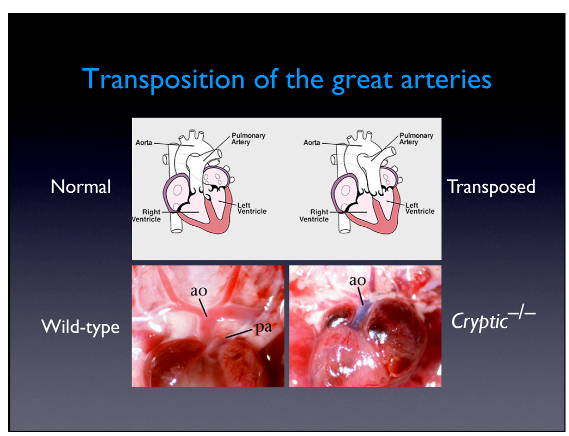

Stages of L-R laterality determination
Initial symmetry breaking
Nodal flow model


Stages of L-R laterality determination
Initial symmetry breaking
Propagation and maintenance of an asymmetric signal
Specification of tissue-specific laterality
RIGHT
LEFT
Node
Nodal
Lefty1
Primitive streak
Pitx2
Lateral plate mesoderm
Asymmetric gene expression


Asymmetric expression of Nodal and Lefty
Nodal
Lefty
(Beddington and Robertson (1998))


Left-right laterality defects in Cryptic mutants
Cryptic−/−
Wild-type
Wild-type
Cryptic−/−
Cryptic−/−
Wild-type
Cryptic−/−
Wild-type
Cryptic−/−


Cardiac defects in Cryptic mutants
ra
la
rv
lv
asd
asd
Wild-type
Cryptic−/−
Cryptic−/−


Transposition of the great arteries
Normal
Transposed
Aorta
Pulmonary Artery
Right Ventricle
Left Ventricle
Wild-type
Cryptic−/−
ao
pa
ao

Morphological changes at early post-gastrulation stages