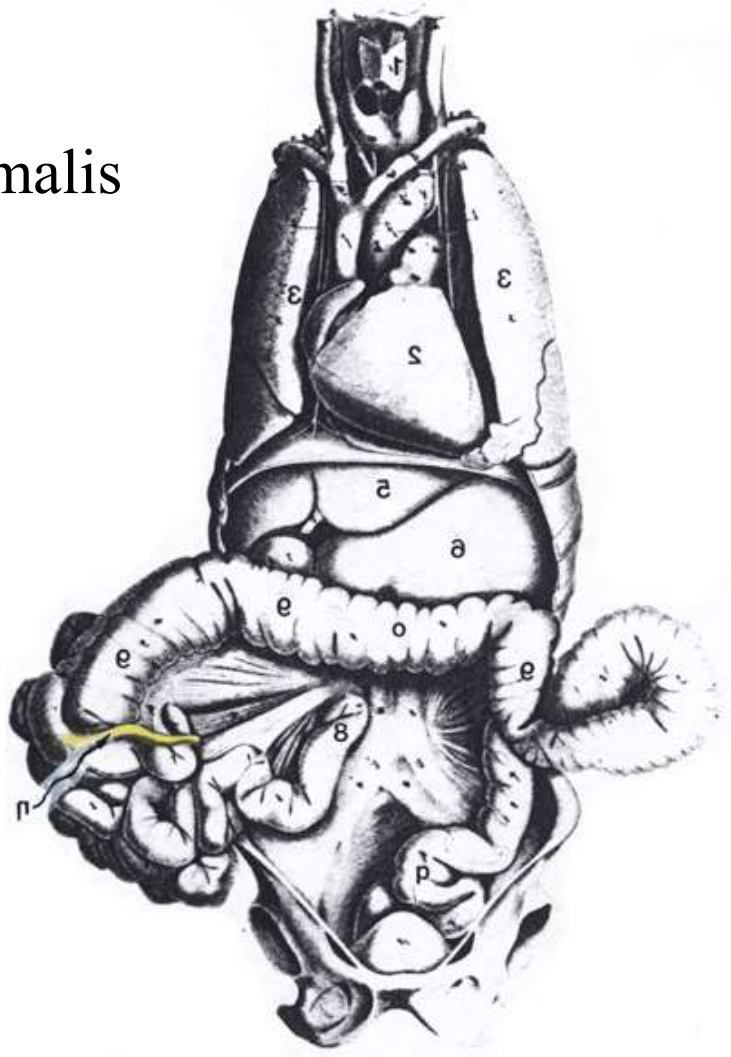
Testtengelyek kialakulása az embryonális fejlődés során

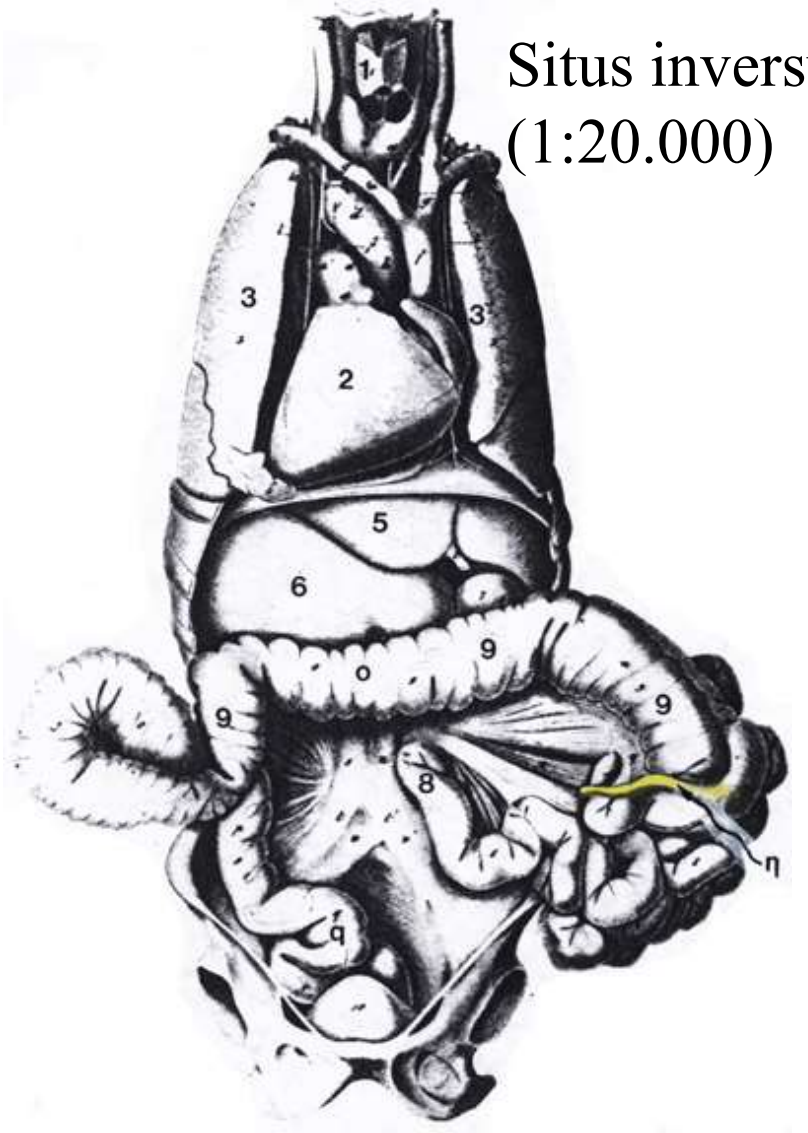
Dr. Nagy Nándor

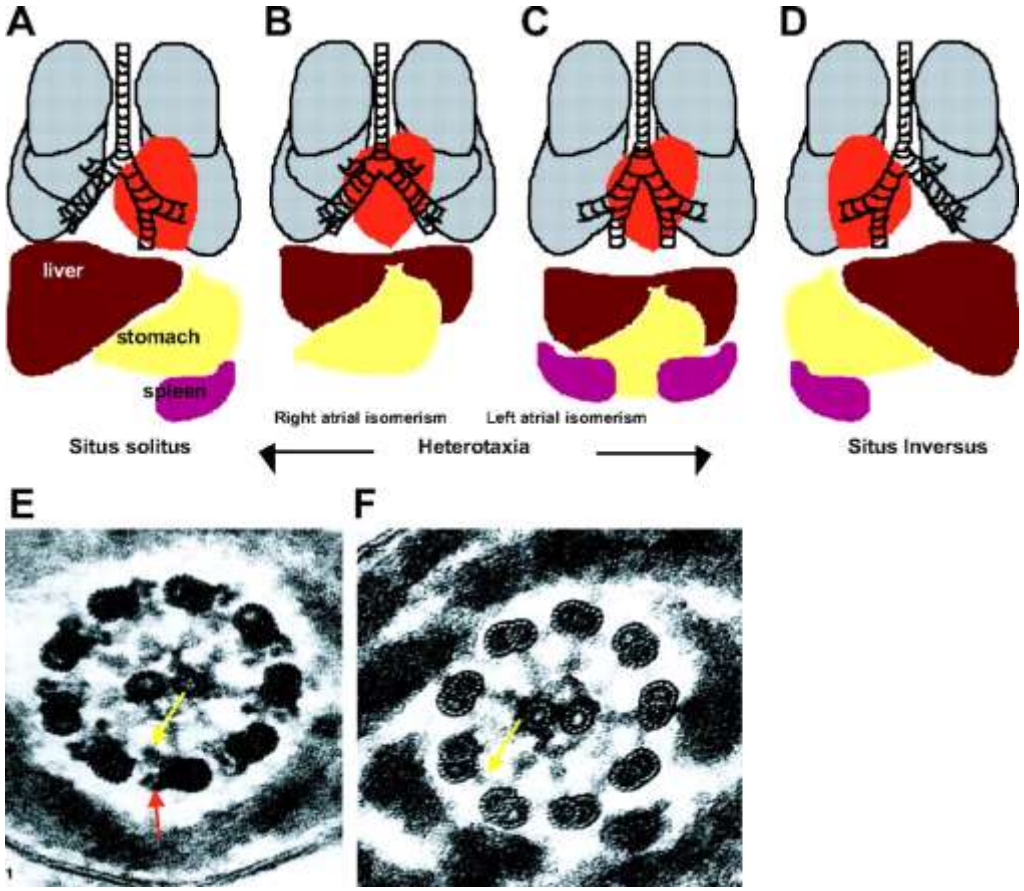
Semmelweis Egyetem

normalis



Situs inversus
(1:20.000)

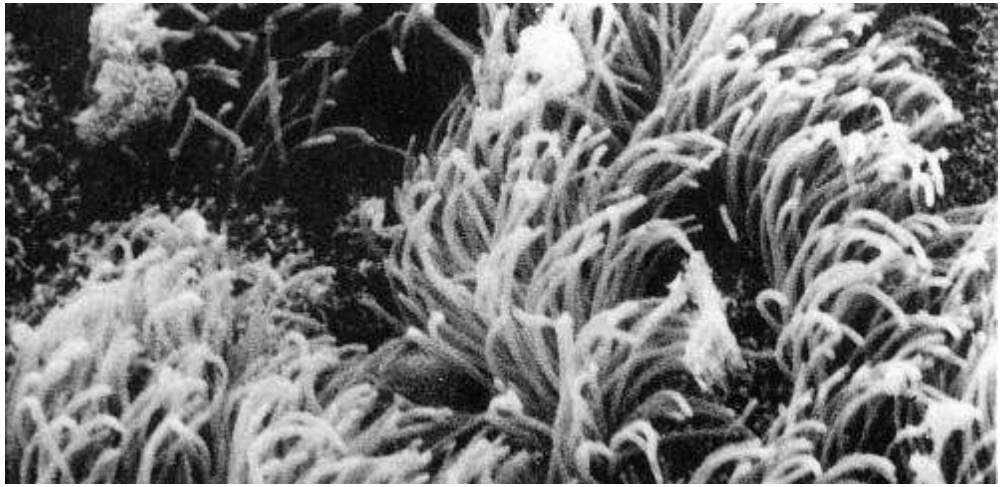




A, Situs solitus. B, Right atrial isomerism. The liver is midline, there are 2 eparterial bronchi, the position of the stomach and cardiac apex is indeterminate, and there is asplenia. C, Left atrial isomerism. The liver is midline, there are 2 hyparterial bronchi, the position of the stomach and cardiac apex is indeterminate, and there are multiple spleens. D, Situs inversus. Ciliary defects in PCD. E, Normal cilium. The outer dynein arms are indicated by a red arrow, and the inner dynein arms are indicated by a yellow arrow. F, Cilium in a patient with PCD. Note the absence of outer dynein arms.

-**Kartagener's syndrome,**
-dextrocardia,

-situs inversus (1:10.000, a complete mirrorimage reversal of the sidedness of asymmetrically positioned organs and asymmetric paired organs),

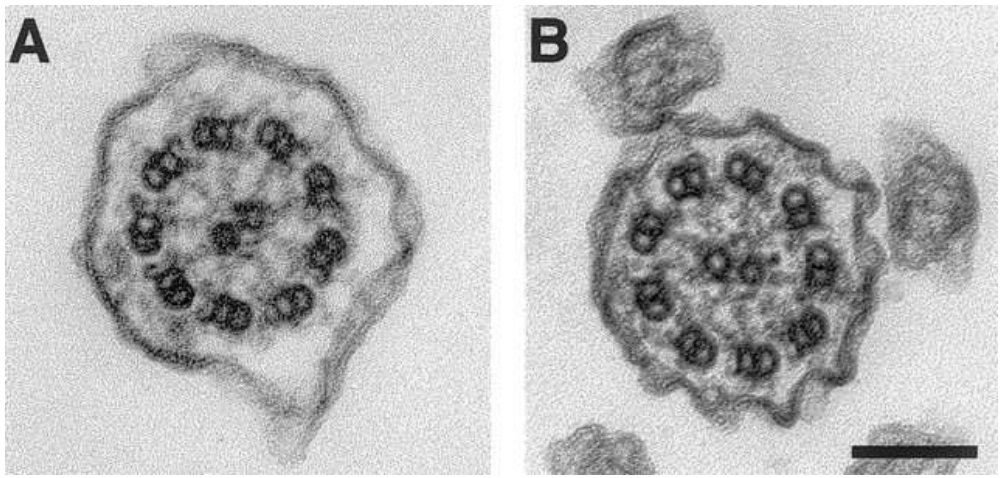


Kartagener syndromea

DYNEIN AXONEMAL HEAVY CHAIN 5 (*DNAH*5) mutációja

Mozgásképtelen csillók, spermiumok

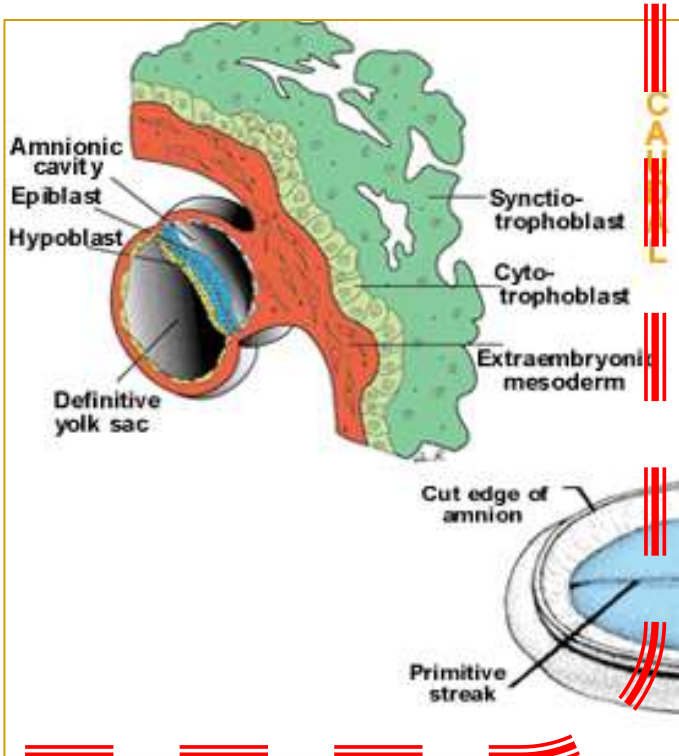
50:50 % situs inversus



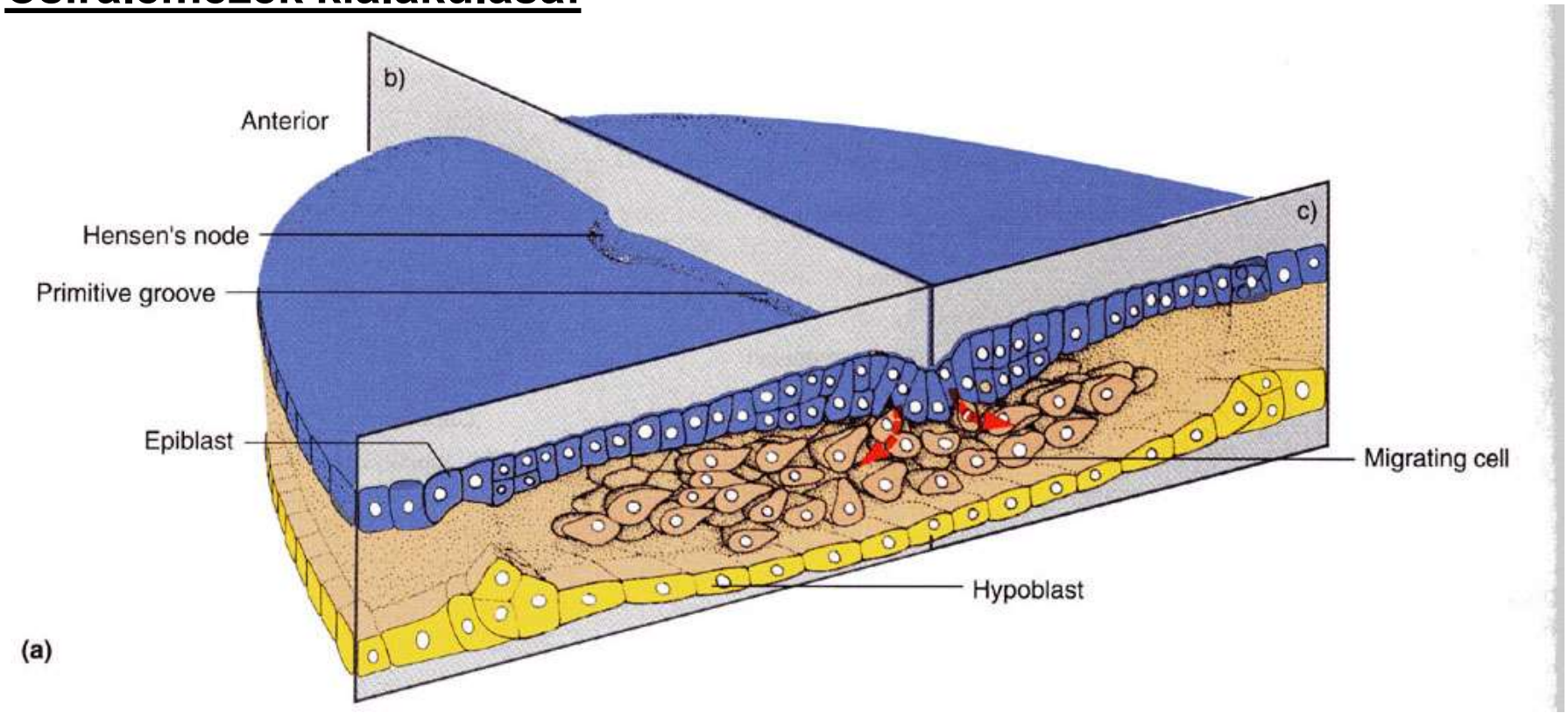
Miért fontos a gasztruláció?

- Csíralemezek kialakulása:
  - Ektoderma, mezoderma és entoderma

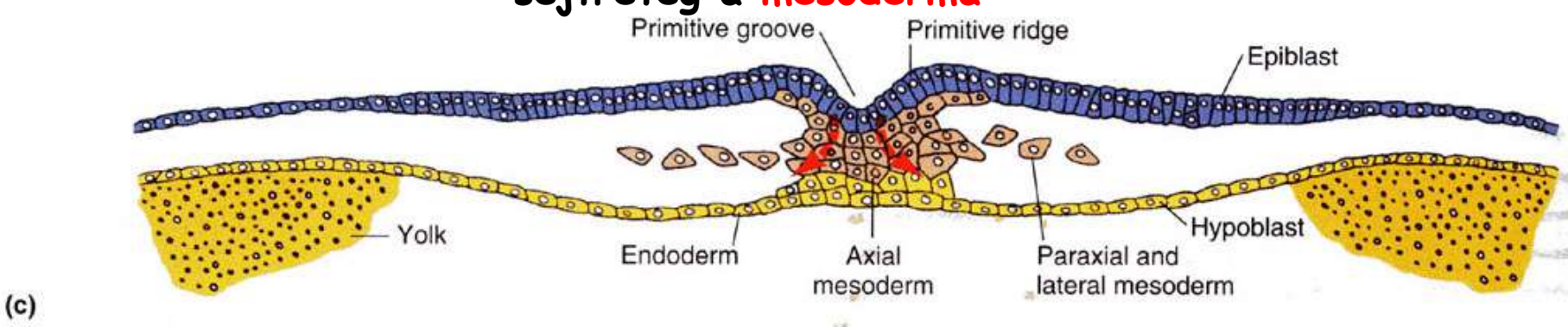
- Testtengelyek kialakulása:
  - Anterior - posterior
  - Dorsal - ventral
  - Bal - jobb



Csíralemezek kialakulása:



-a két elsődleges csíralemez, az ectoderma és az endoderma közé benyomuló sejtréteg a mesoderma



***Brachyury* mRNA (T-box) expression containing transcription factor**

The *brachyury* mutation was first described in mice

-affects tail length and sacral vertebrae in heterozygous animals and is lethal in homozygous animals around embryonic day 10 due to defects in mesoderm formation, notochord differentiation and the absence of structures posterior to the forelimb bud).

Gastrulation Anomalies

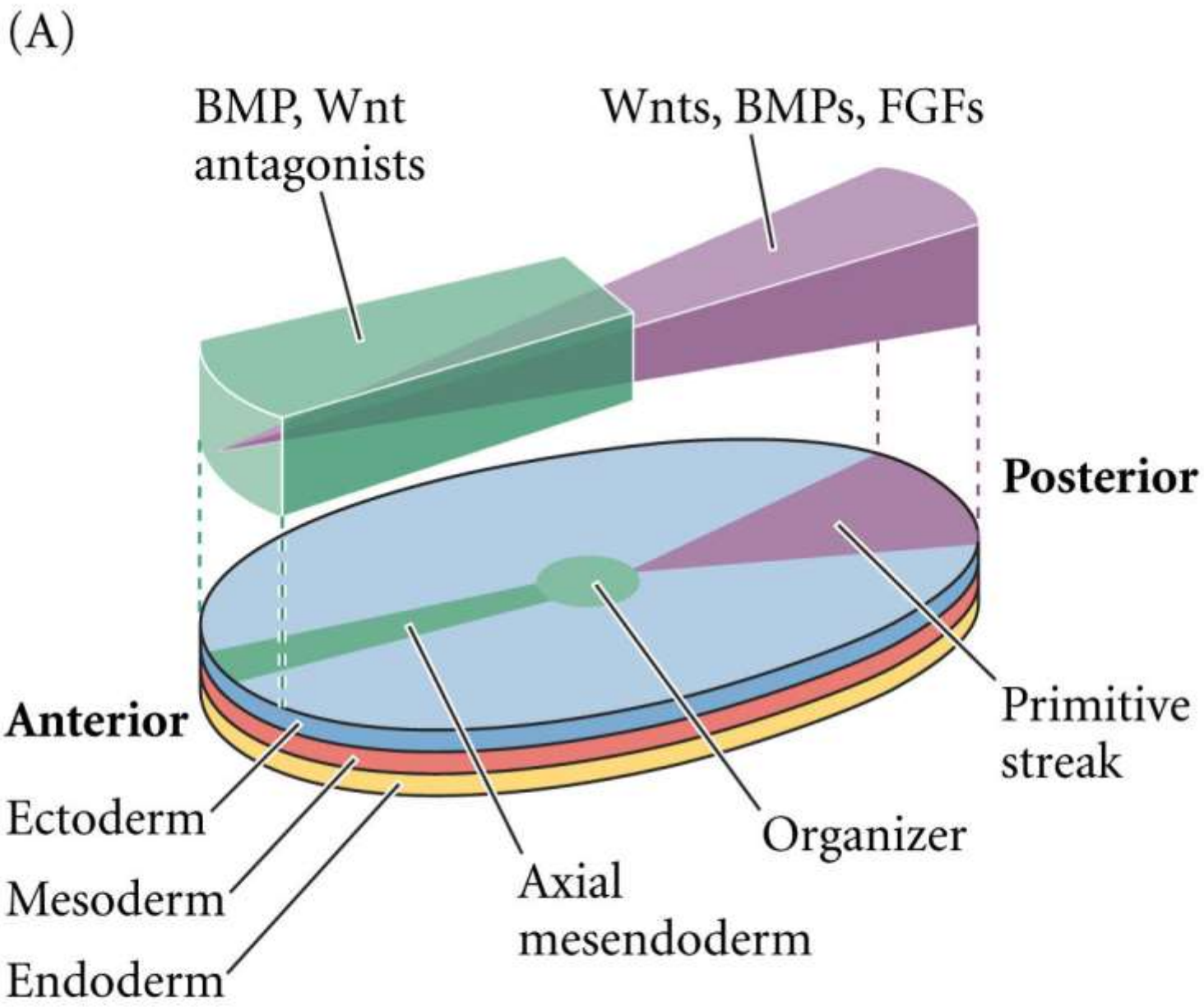
Caudal Dysgenesis (Sirenomelia)

-Caudal defect: Insufficient mesoderm formation

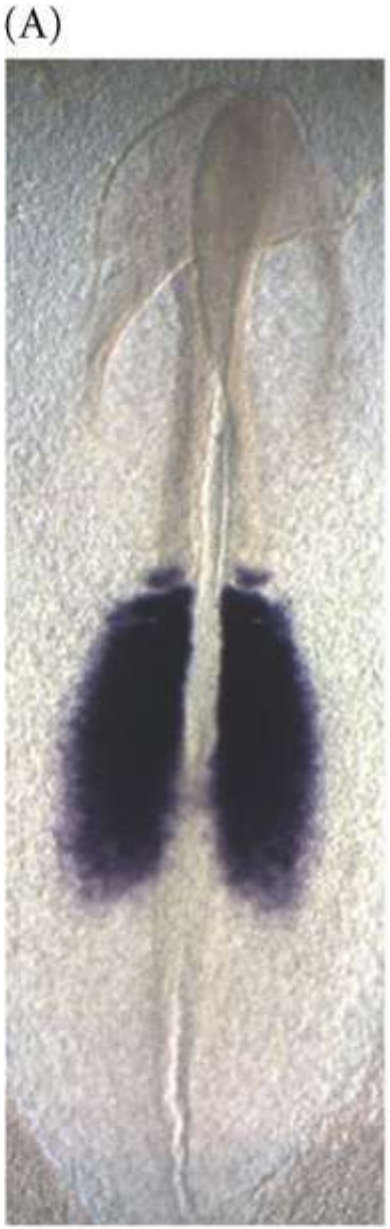
-Fused lower limbs, renal agenesis

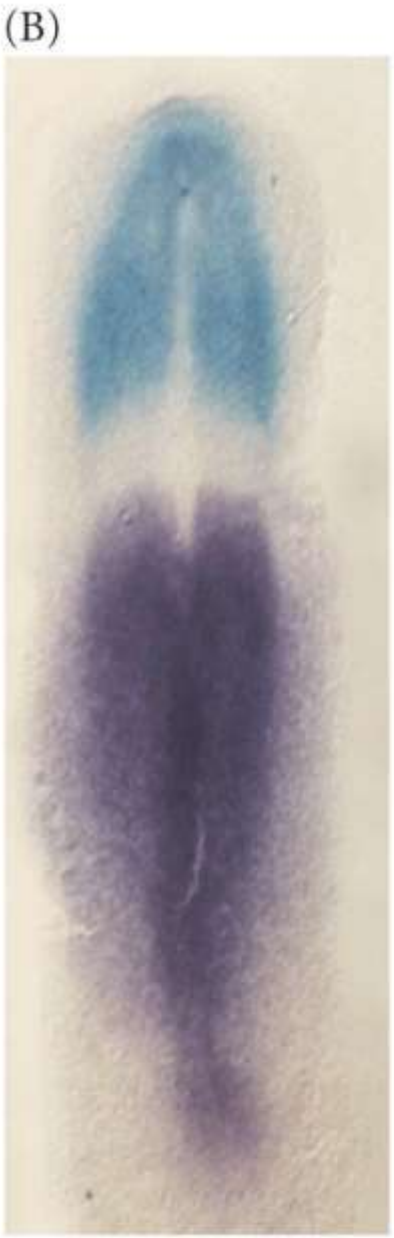
-Genetic and teratogenic mutation of Brachyury (T) gene (*the brachyury mutation was first described in mice affects tail length and sacral vertebrae in heterozygous animals and is lethal in homozygous animals around embryonic day 10 due to defects in mesoderm formation)*

Anterior-posterior patterning in the mouse embryo

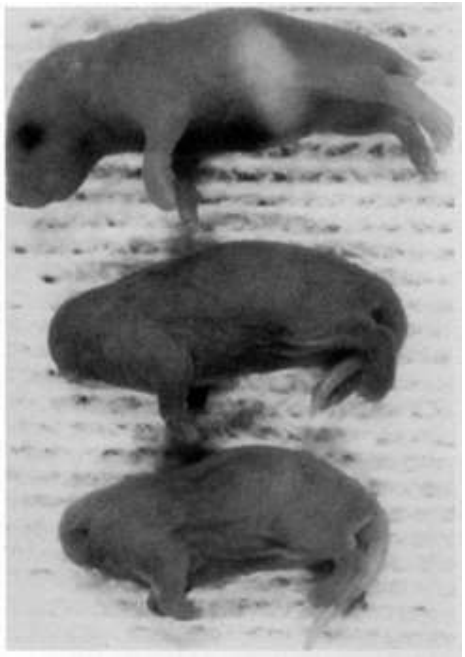


Anterior-posterior tengely





Wnt-antagonista mutáns egér embryok



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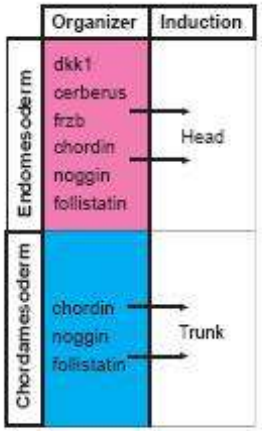
head induction requires the inhibition of both BMP and Wnt signals *(Glinka et al. 1997).*



Role of *dickkopf1* in the head organizer

Fig. 1. Two-inhibitor model for Organizer regionalization. *Trunk induction requires inhibition of BMP-signalling while head induction requires dual inhibition of Wnt and BMP-signalling. The organizer produces factors that inhibit both types of signals (anti-wnt: Dkk1, Cerberus, Frzb; anti-BMP: Cerberus, Noggin, Chordin, Follistatin). Regional specificity of induction results from differential expression of Wnt- and BMP-inhibitors in endomesoderm and chordamesoderm. Note that Cerberus inhibits also Nodal and Activin signalling, which may be important to maintain anterior endomesodermal fate.*

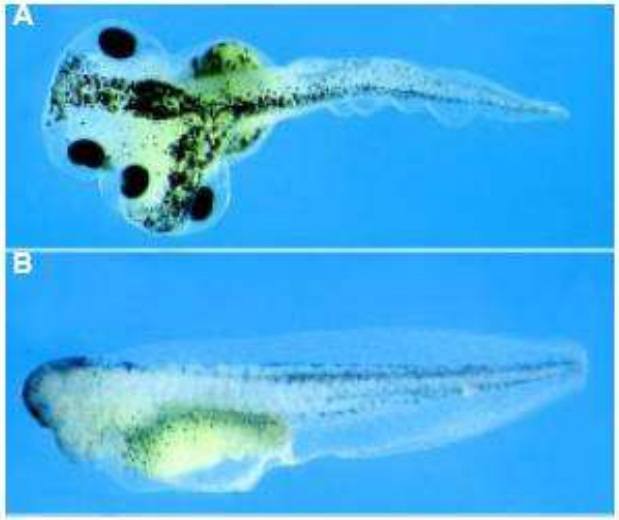
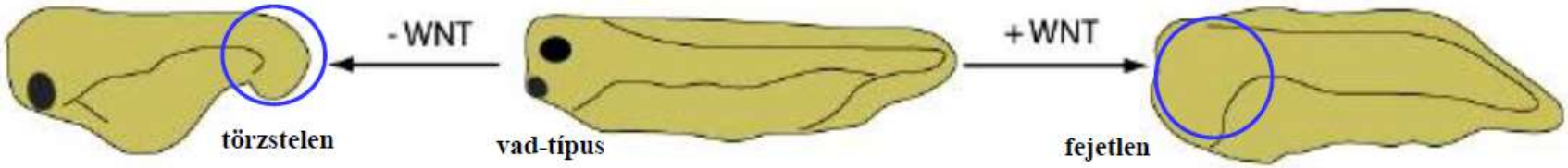
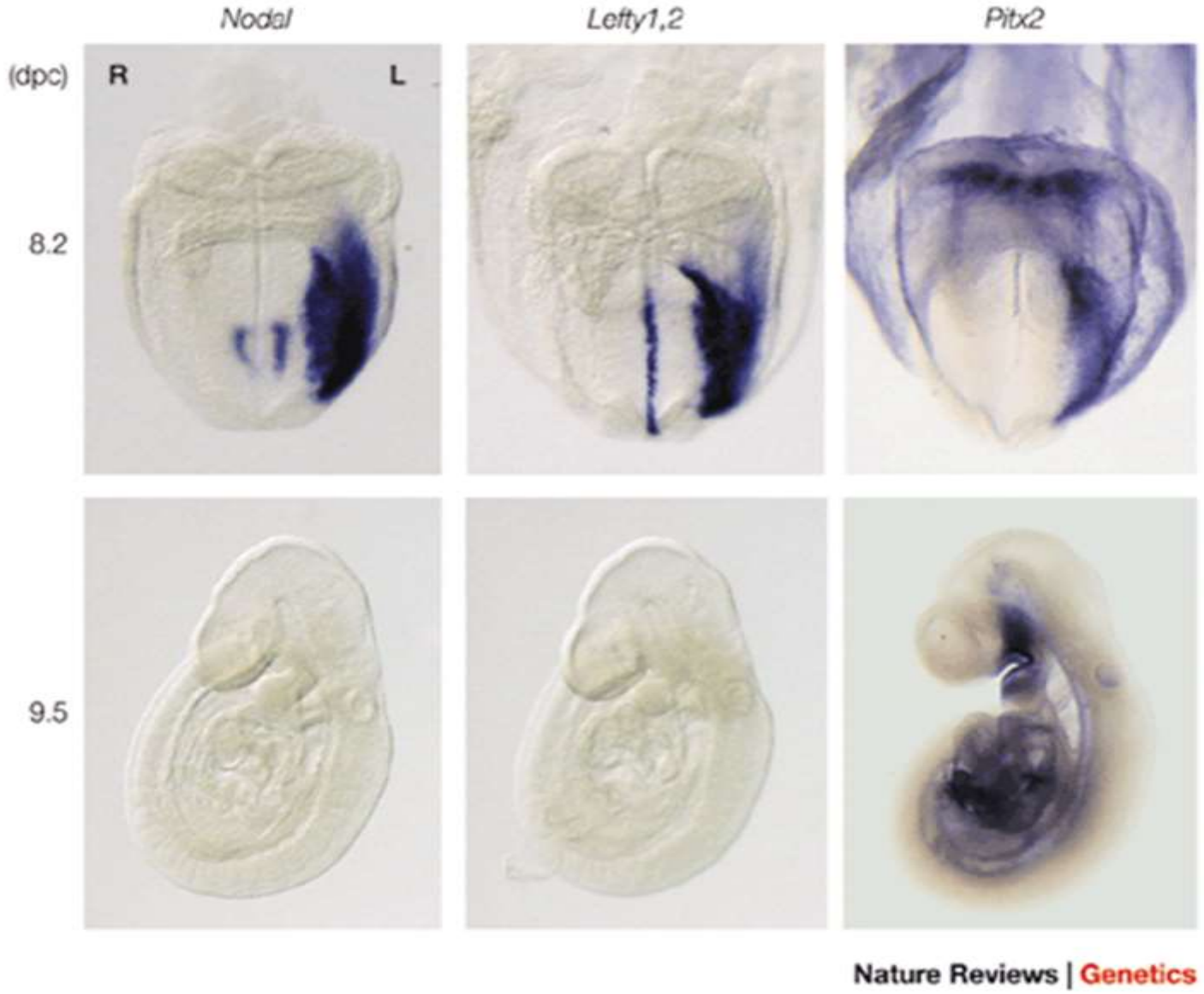


Fig. 3. Head induction by *dickkopf1*. (A) *A tadpole-stage embryo that has been injected with mRNA encoding a dominant-negative BMP receptor (tBR) and dkk1 forms a complete secondary head.* **(B)** *A tadpole embryo microinjected with inhibitory anti-Dkk1 antibodies. The experimental embryo lacks anterior head structures (Glinka et al., 1998 and unpublished).*

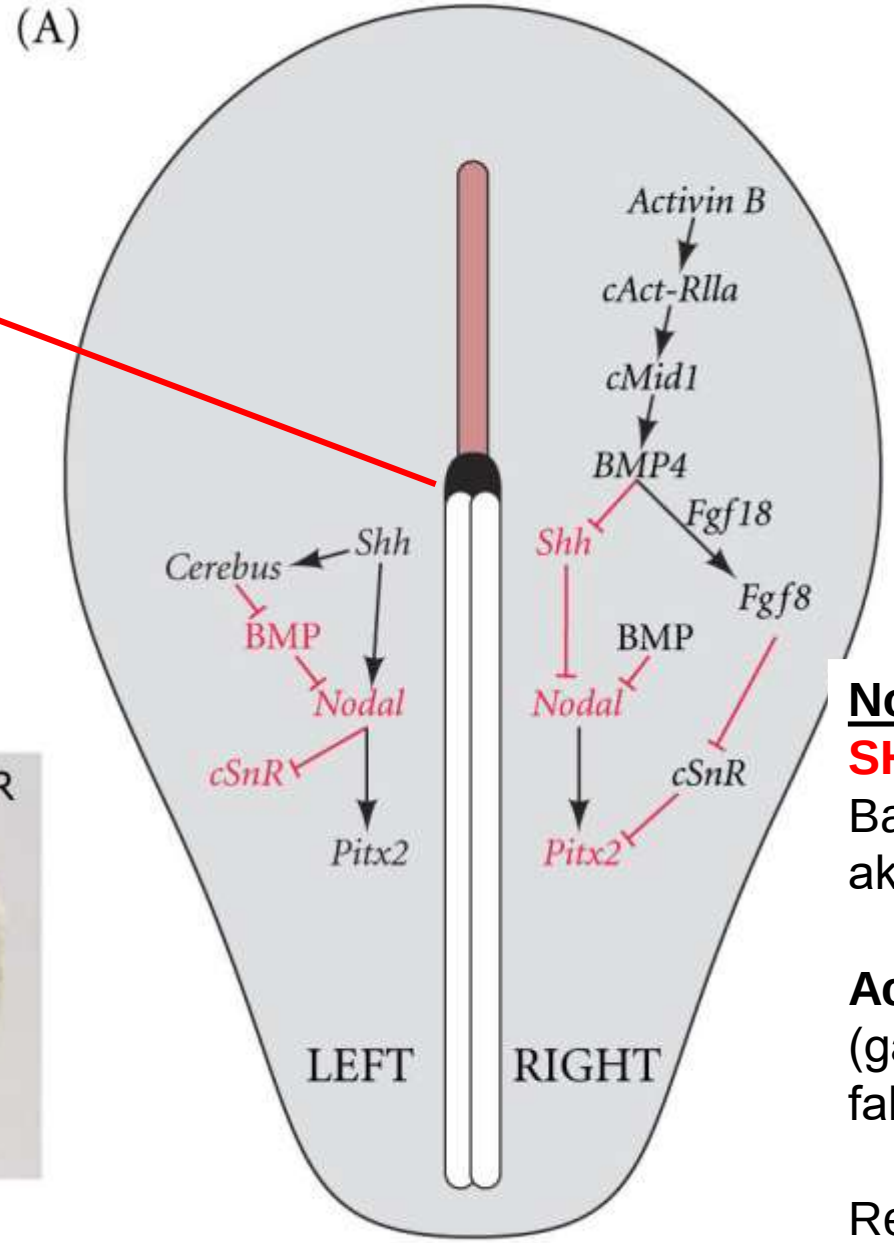
- a helyes Wnt mennyiség jelentősége

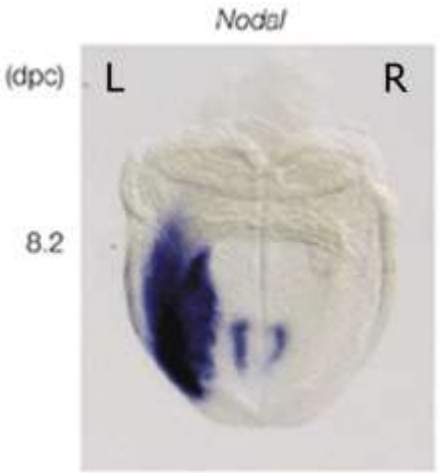


Pathway for left-right asymmetry in the embryo



Primitív gödör





Node Signals:

SHH – Sonic Hedgehog – Bal oldalon a NODAL-t aktiválja

Activin – jobb oldalon (gátolja a SHH növekedési faktor aktivitását)

Reverse Asymmetry = situs inversus

Situs inversus és a csillók

Az embryo-csomó kb. 200 sejtjén monocilium van.

A középső területen motilis 9+0 csillók, **köröző mozgás,**

jobbról-balra tartó folyadékáramlás.

Szélen primer csillók, a sejtekben Ca-szint emelkedés.

A balra tartó áramlás szükséges a normális situs létrejöttéhez.

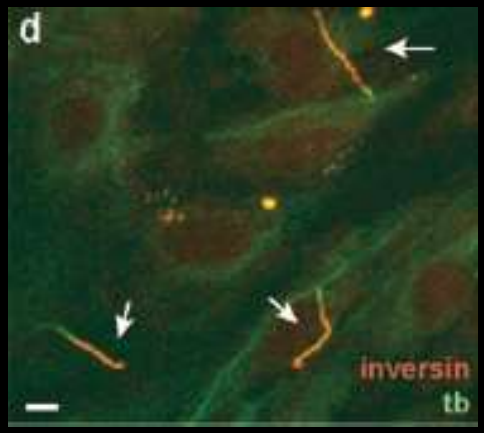
In vitro kísérlet: folyadékáram megfordítása → situs inversus

Kétféle magyarázat:

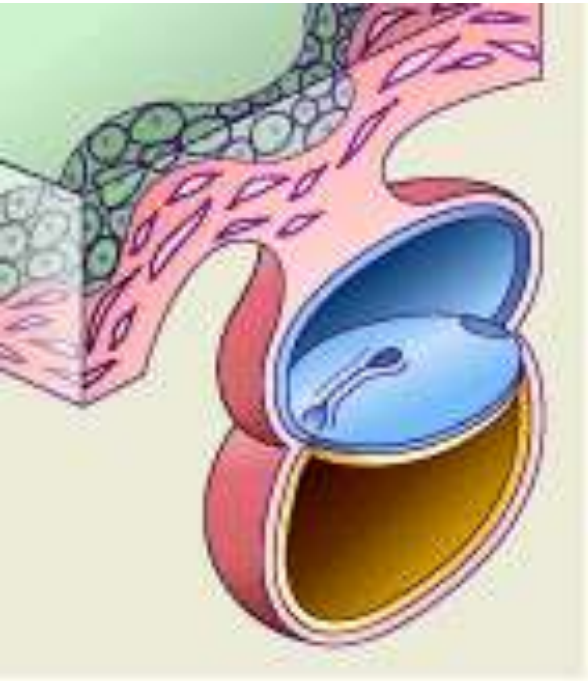
- **morphogen koncentrációgrádiens**
- **széli primer csillók mechanoreceptorok, megdőlésük**

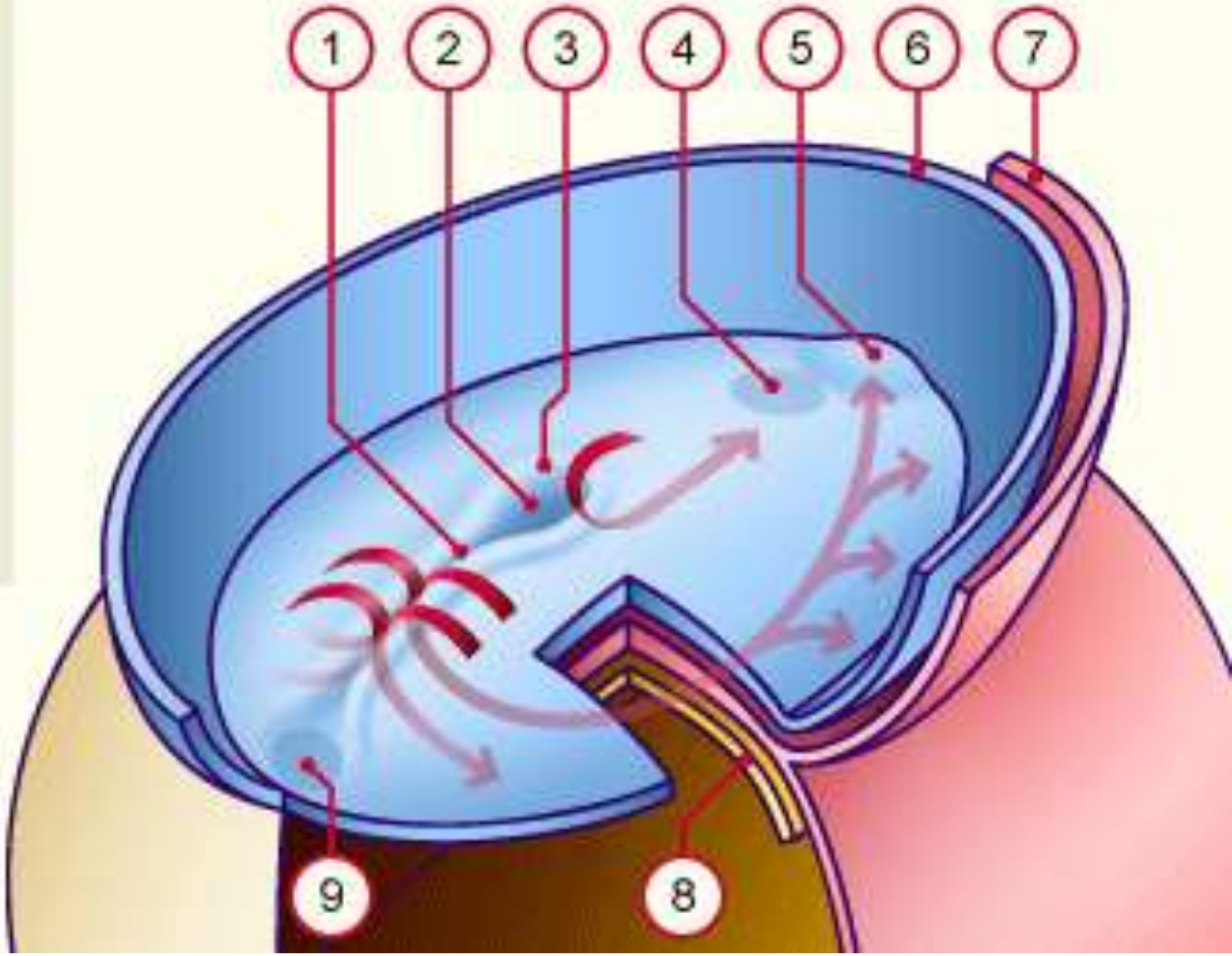
  Ca-csatornát nyit ki (polycystin-2 kimutatható!).

Inversin (NPHP2, egy csillófehérje) hiányában situs inversus jön létre, ugyanakkor vesecysták is a kéreg-velő határon (2. típusú nephrophthisis).



vesehámsejtek

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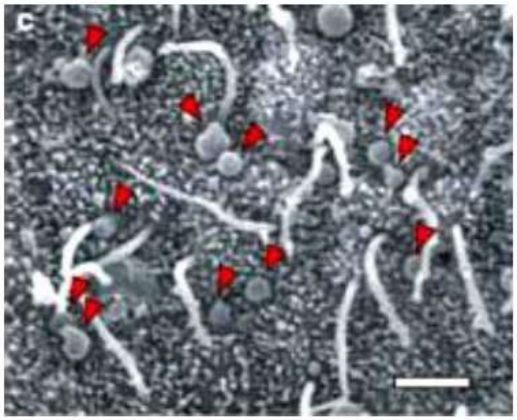
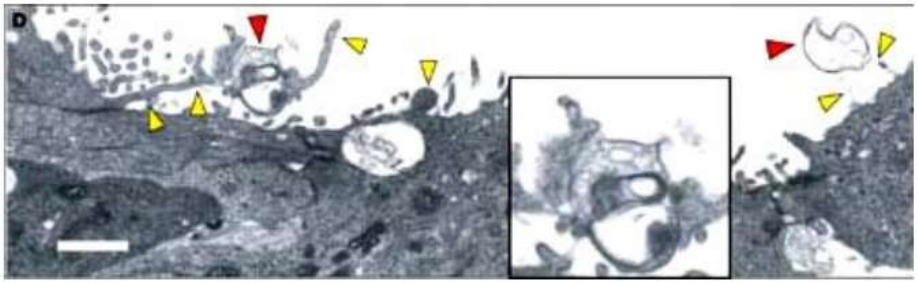
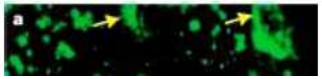


A nodális gödör felszíne – SEM:
NVP-k (piros nyílhegy) és csillók

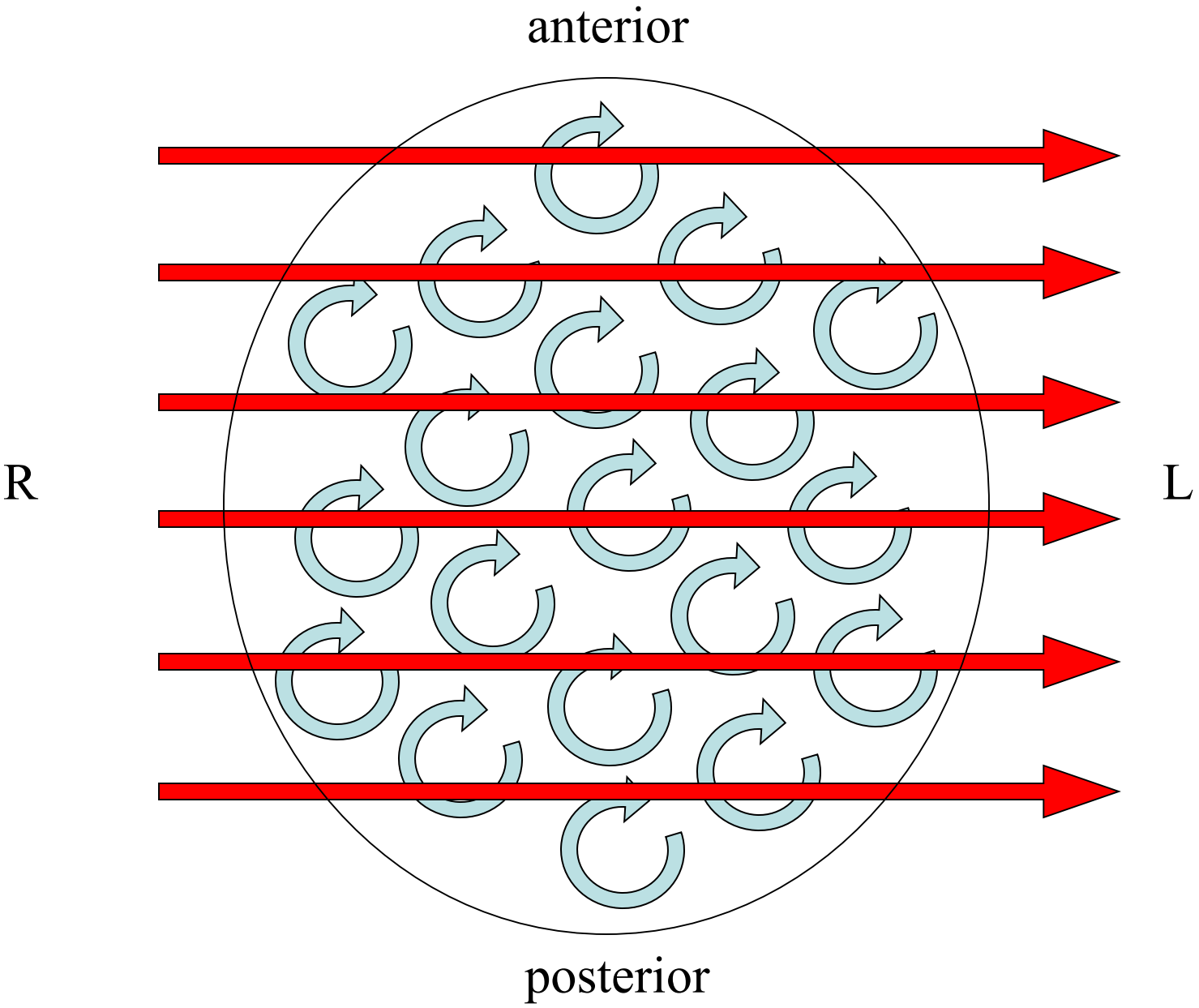
● NVP-k és ostorok



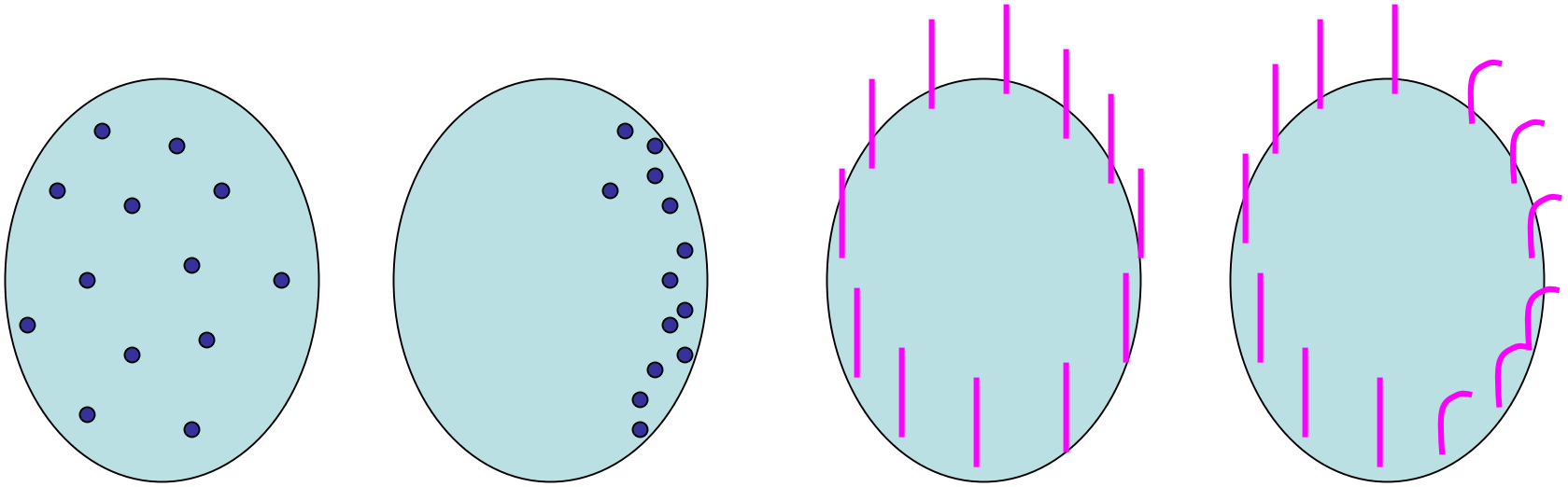
A nodális gödör felszínének keresztmetszete (TEM):
képződő NVP-k (piros nyílhegy),
csillóhoz tapadt NVP-k (sárga nyílhegy)



1. Mechanosensoros modell; 2: morfogén áramlás; 3: vezikuláris transzport

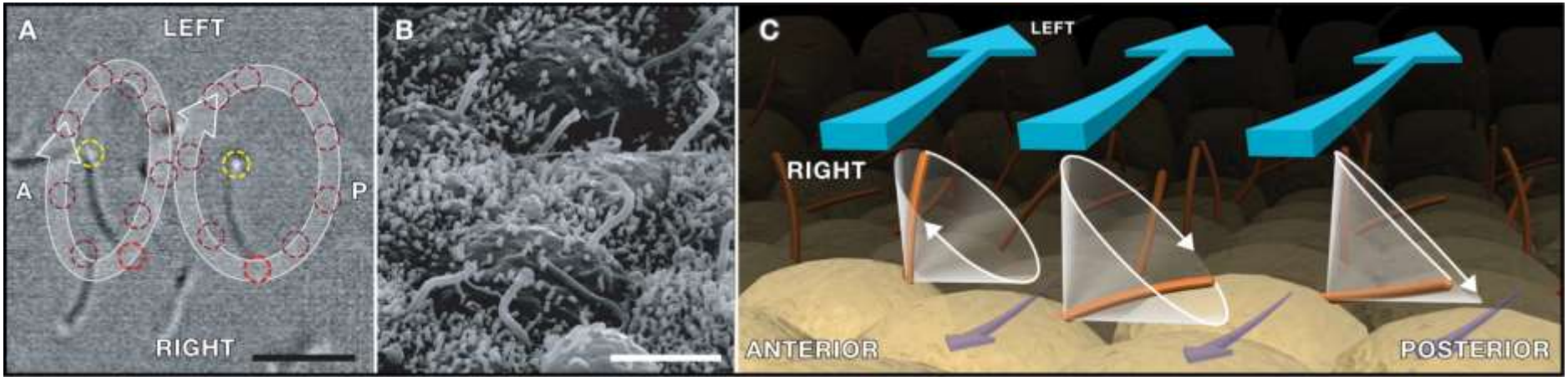


How does fluid flow influence nodal/lefty2 switching?

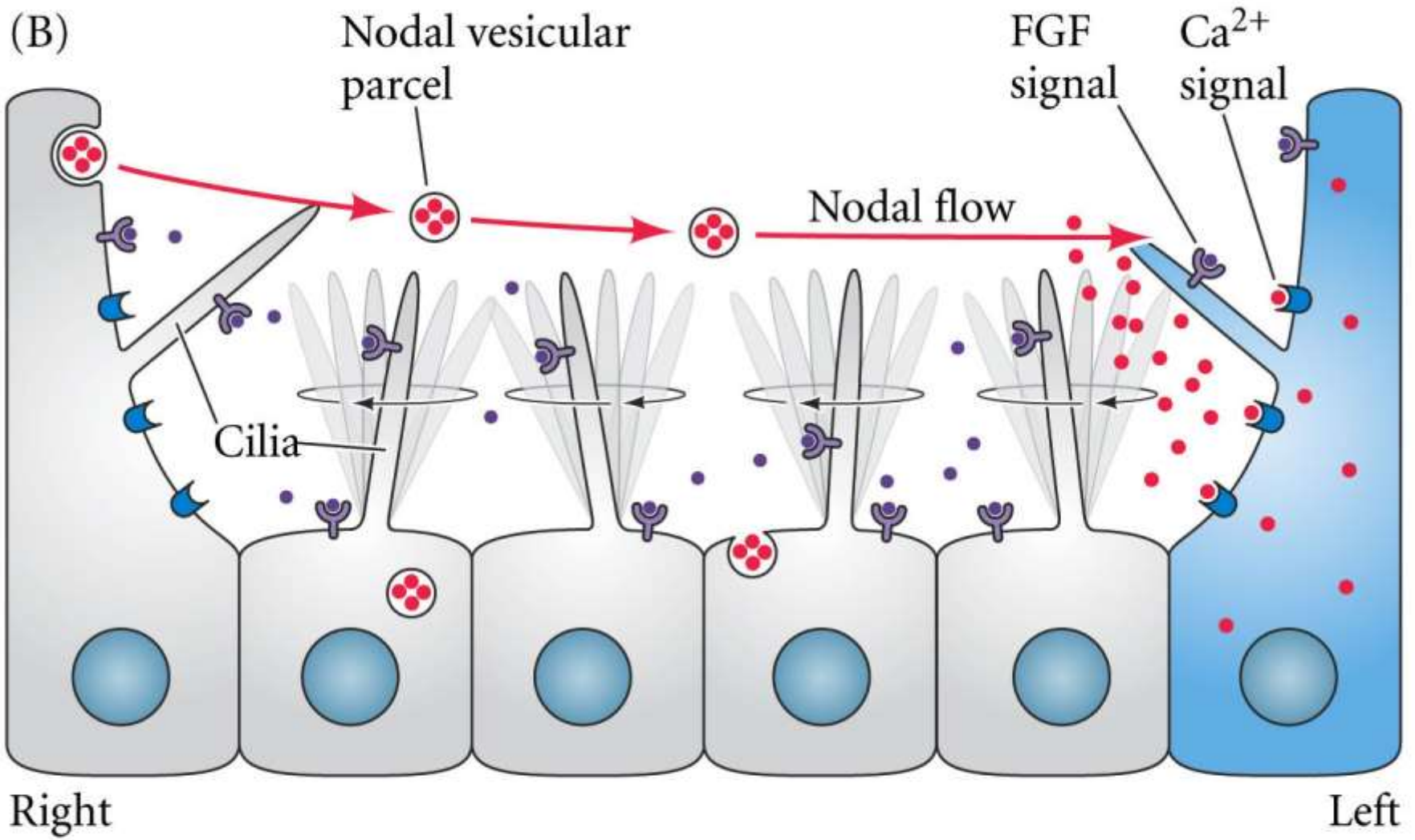


Morphogen sweeping

Mechanosensory cilia



nodal flow model (áramlás modell) a jobb-bal aszimetria kialakulásra



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JOBB-BAL ASZIMMETRIA
situs inversus

***Inversion of embryonic turning (inv)*:**

aszimmetrikus szervek tükörkép elhelyezkedése

nodal, lefty, Pitx2:

jobb oldalon

Situs inversus viscerum (iv):

aszimmetrikus szervek véletlenszerűen jobb vagy bal oldaliak

nodal, lefty, Pitx2:

jobb vagy bal oldalon

mindkét oldalon vagy egyik oldalon sem

dynein defektus: csillók nem mozognak

Kartagener-szindróma:

légúti hámsejtek csillói, spermiumok mozgásképtelenek – dynein defektus

idült légúti infekciók

meddőség

situs inversus