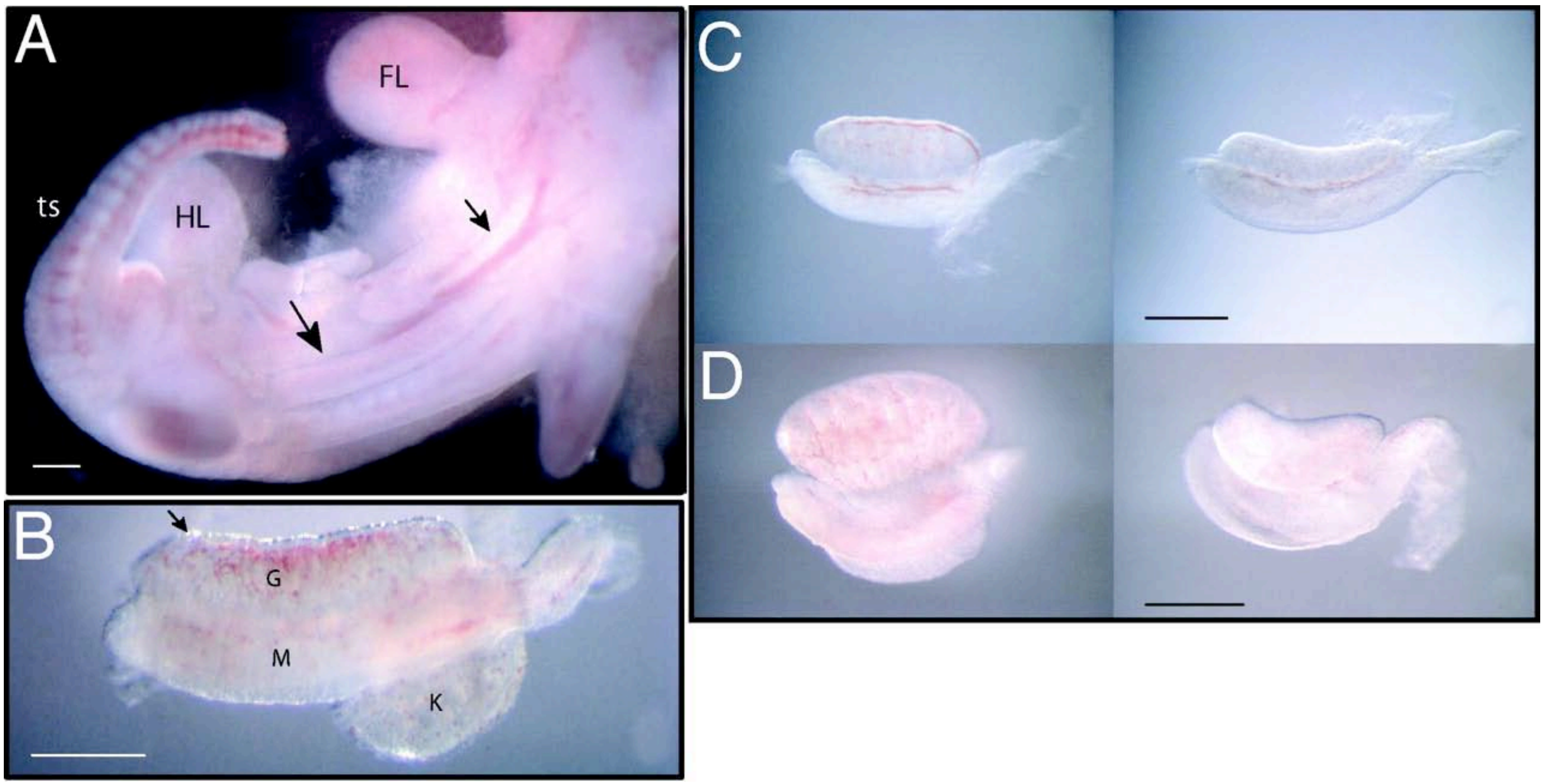
Embryology of the Testis



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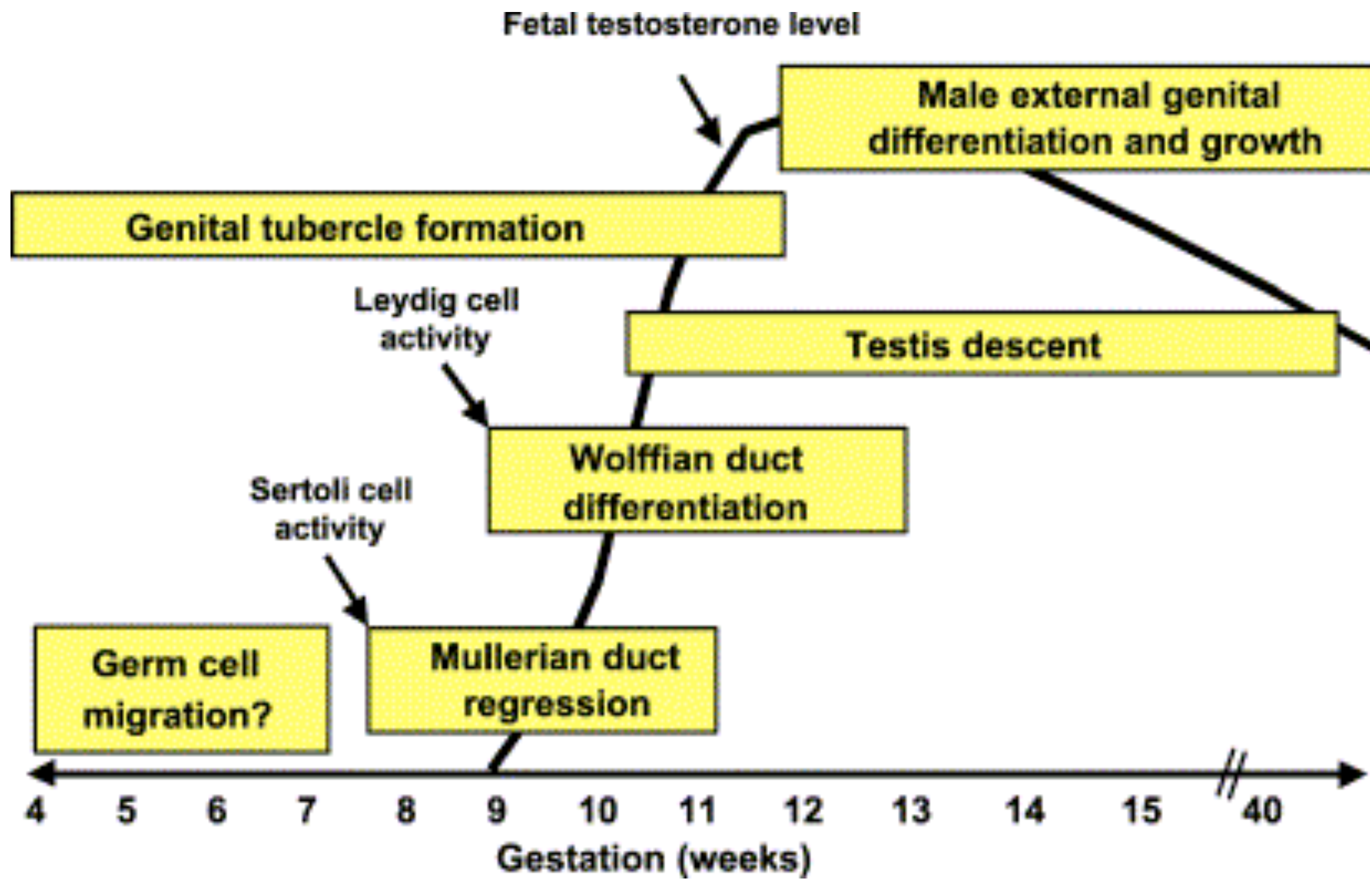
Human Testicular Development



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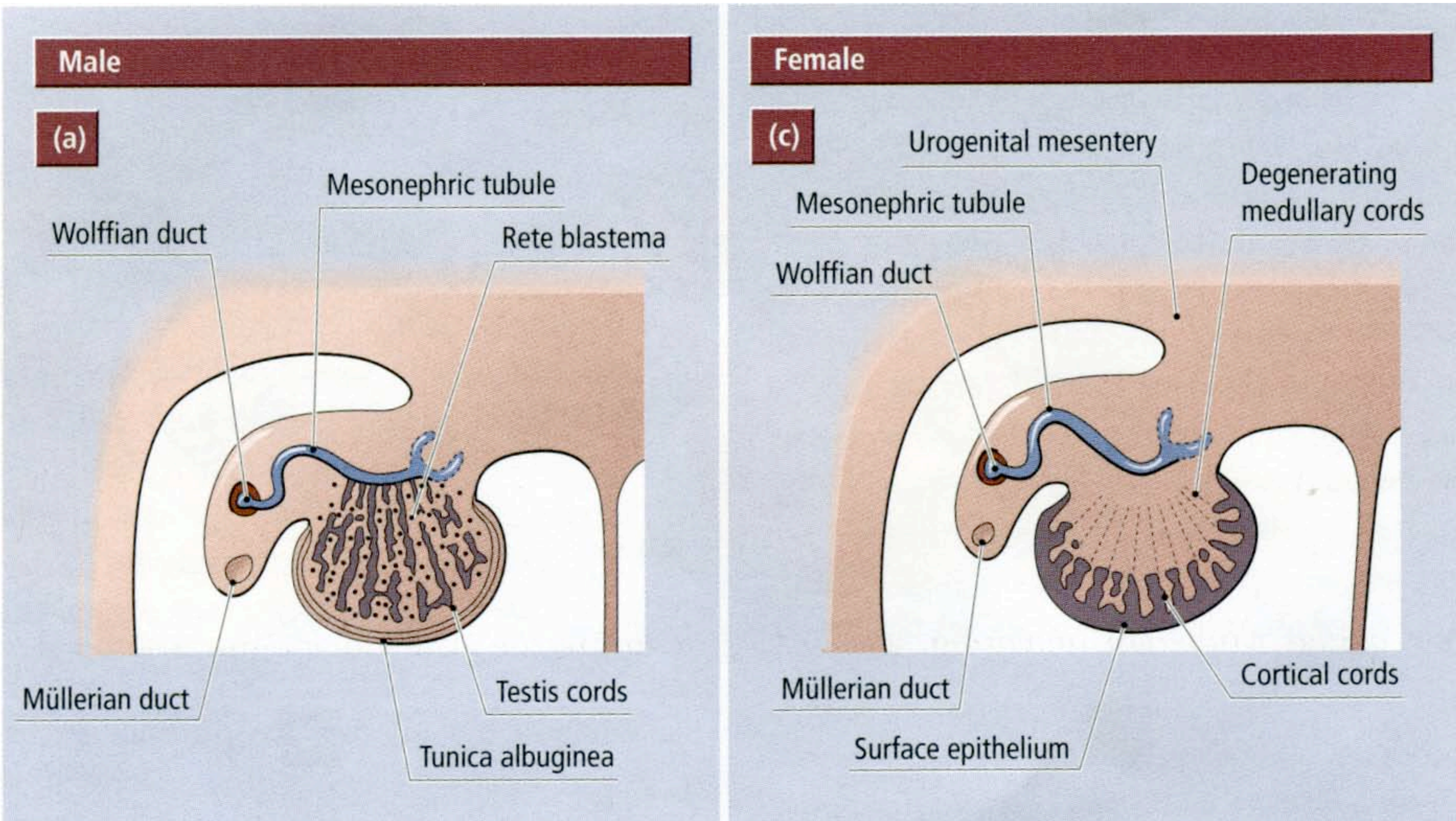
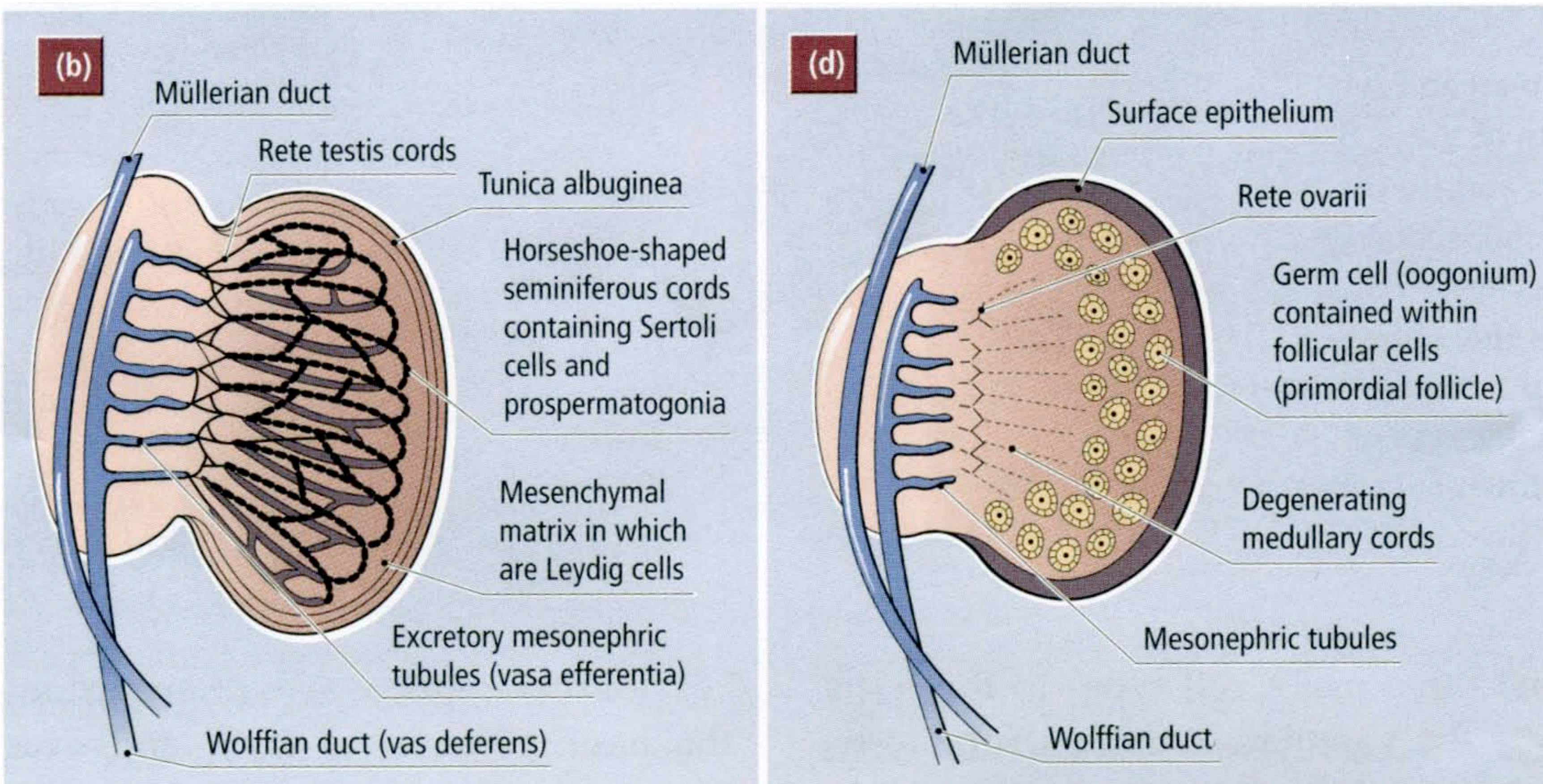
8 week human

Medulla: inner part
Cortex: outermost layer

7 week human





16-20 week human

20-24 week human

Cell Lineages in Testis & Ovary

Table 1. Cell lineages in the indifferent gonad and their fates after sex differentiation.

Indifferent gonad	Testis	Ovary
Supporting	Sertoli	Granulosa
Steroidogenic	Leydig	Theca
Stromal	Peritubular	Stromal
Gonocytes	Spermatogenesis	Oogenesis
Unknown	Macrophages	Not present

Soder (2007) Best Practice & Research Clinical Endocrinology & Metabolism 21: 381–391.

Timing of Major Testicular Events in Mammals

- Variation among mammals in timing
- Process similar

Species	Genital ridge formation	Testis formation	Beginning of transabdominal phase	Beginning of inguinoscrotal phase	Testis in scrotum
Human (270)	49 (18%)	56 (21%)	70 (26%)	182 (68%)	245 (91%)
Pig (115)	21–22 (18–19%)	27 (24%)	55 (48%)	85–90 (74–78%)	around birth
Horse (336)	30 (9%)	34 (10%)	45 (13%)	ca. 310 (92%)	around birth
Cattle (281)	30–32 (11%)	41 (15%)	80–90 (29–32%)	112 (40%)	around birth
Sheep (149)	22 (15%)	31 (21%)	60–65 (40–44%)	72–75 (48–50%)	around birth
Dog (65)	23–24 (35–37%)	29 (45%)	42 (65%)	4–5 dpp (106–107%)	35–40 dpp (154–162%)
Mouse (20)	9.5 (48%)	12 (60%)	15.5 (78%)	6 dpp (130%)	21 dpp (205%)
Rat (22)	9.5 (43%)	12 (55%)	16 (73%)	6 dpp (127%)	19 dpp (186%)

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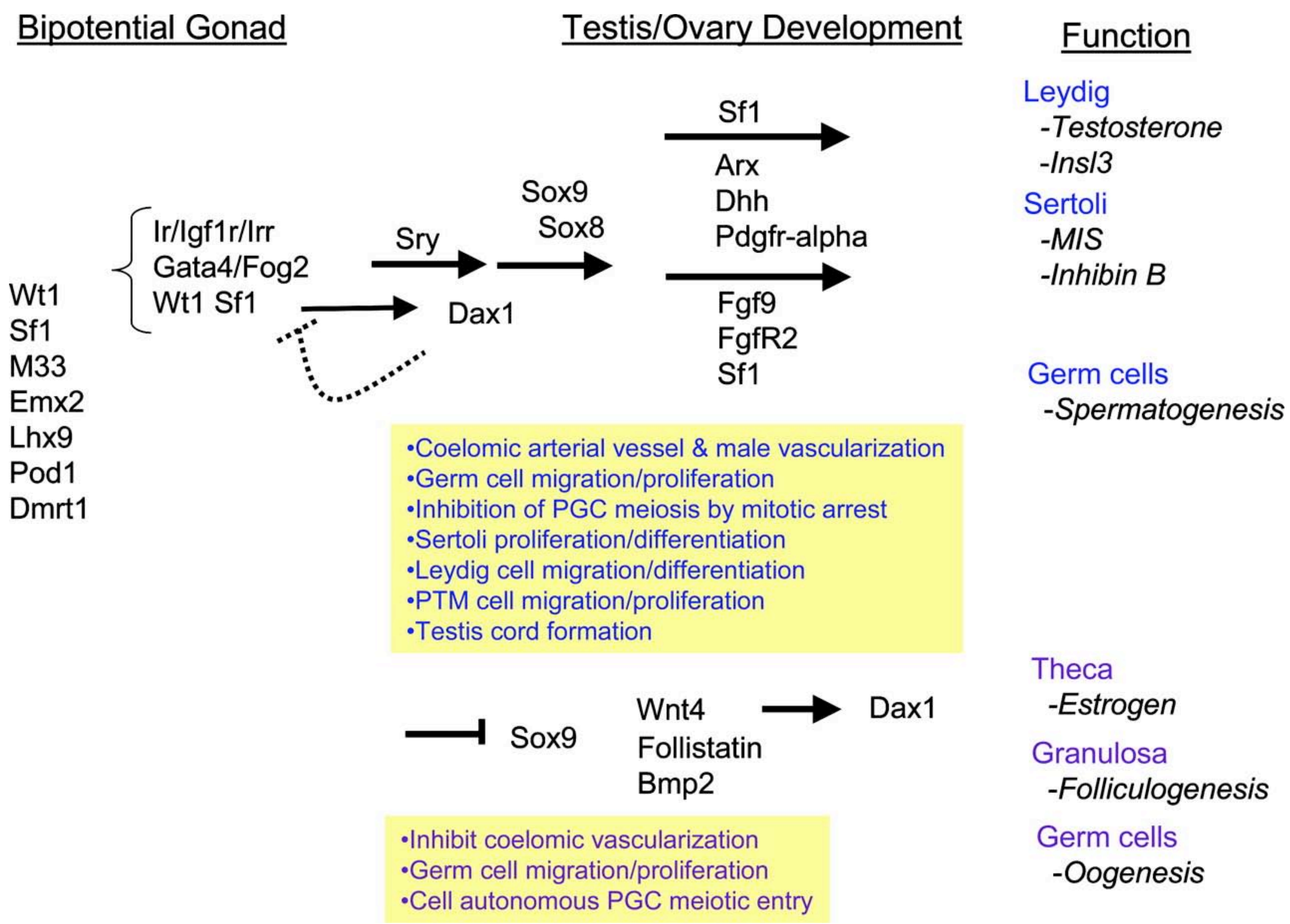
Genes - Ovary/Testis Development



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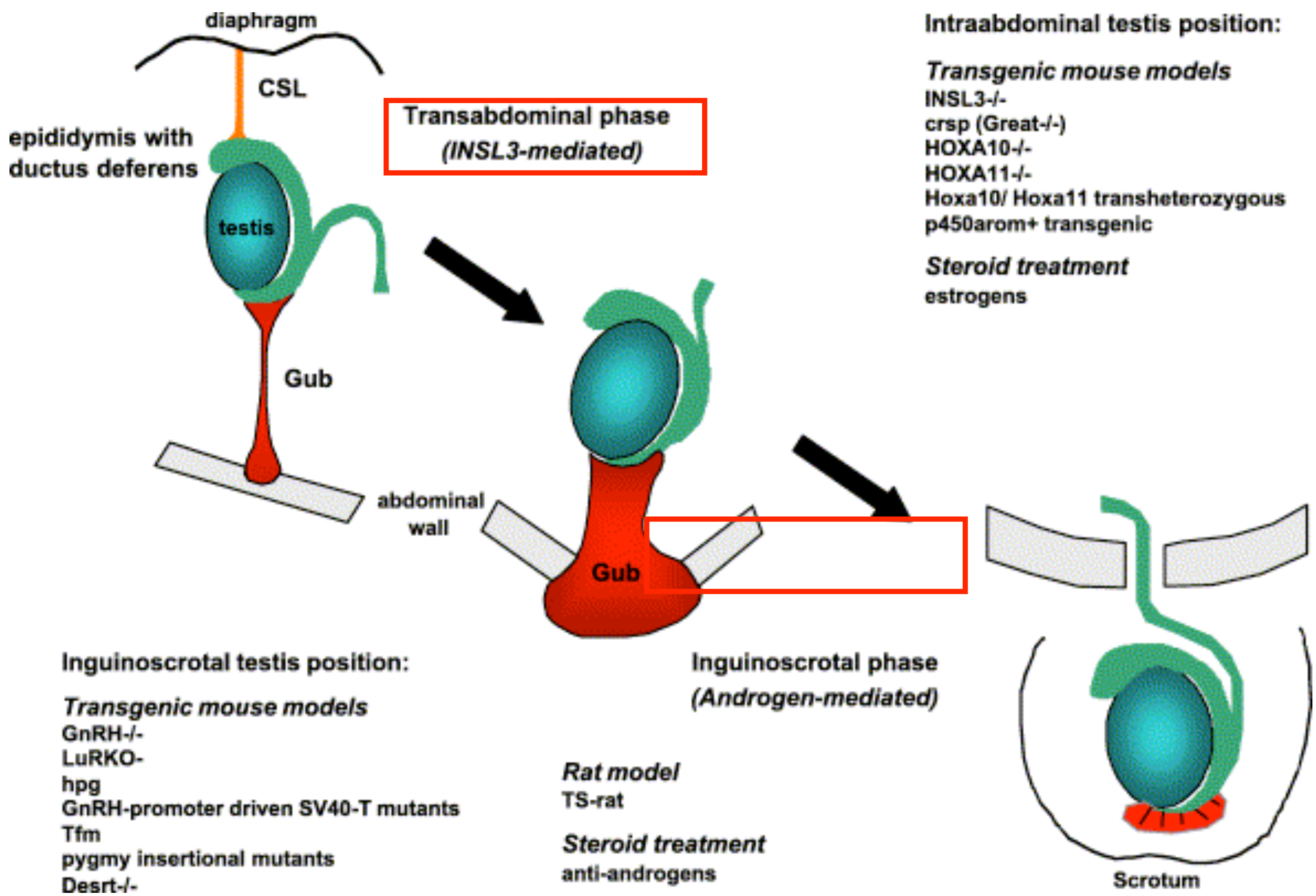
Scrotum

- in most adult mammals testis lies in the **scrotum**
  - migrates there through the body wall - **inguinal canal**
  - some exceptions:
    - testis is lumbar - monotremes, elephants, hyraxes
    - inguinal canal - hedgehogs, moles, some seals
    - seasonal migration - wild ungulates, most rodents

Cryptorchidism

- cryptorchidism - "hidden" "abdominal" testis
  - Undescended testis in those species with scrotal testis
  - detrimental to spermatogenesis and normal testicular metabolism
  - associated with increased risk of testicular cancer
  - rise in US & Europe in last 30-40 years

Descent of the Mammalian Testis



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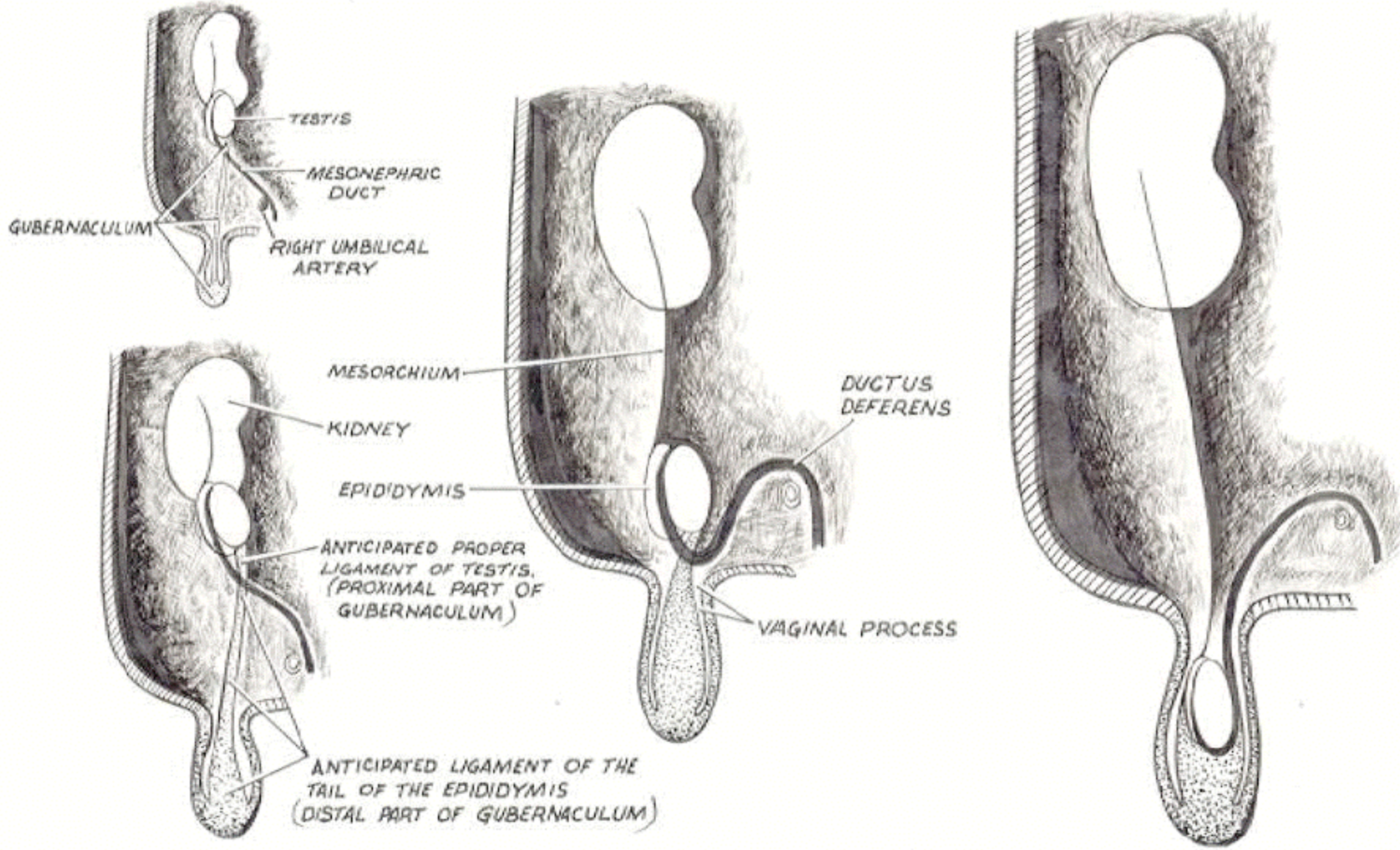
Model for testicular migration

- 1) migration of testis apparently involves two phases
  - Initial stage is transabdominal migration
  - Second stage is passage through the inguinal canal
- 2) A number of hormones are involved in this process
  - INSL3 (insulin-like peptide hormone 3)
  - Testosterone

Model for testicular migration

- testis is firmly attached to abdominal wall by:
  - a) posterior gonadal ligament
  
  - b) **gubernaculum** (Latin: helm or rudder)
    - as body grows gubernaculum does not grow extensively; thus, testis is drawn downward



A SCHEMATIC DIAGRAM OF THE DESCENT OF THE TESTIS.

Intra-abdominal testicular descent to the inner inguinal ring

- Human: initiated at about 10–14 weeks of gestation to about weeks 20–23
- insulin-like peptide hormone INSL3
  - structurally closely related to relaxin
  - marker of mature testicular Leydig cells
  - G protein-coupled receptor LGR8
- Mouse: Bilateral cryptorchidism in INSL3-/- mice
  - small, undifferentiated gubernacula without a central core of mesenchyme
- Transgenic INSL3-/- male mice
  - Overexpressing INSL3 in pancreatic beta-cells
  - Normal transabdominal testis descent
- Transgenic female mice overexpressing INSL3
  - displayed descended ovaries and inguinal hernia
    - INSL3 expression in the ovary initiated day 6 after birth

testicular descent through the inguinal canal

- Human: completed by week 35 in the human
- Pig: around day 95 of gestation in the pig fetus
- inguinoscrotal,but not transabdominal, testis descent is impaired
  - LH receptor knockout mouse (LuRKO)
    - devoid of LH stimulation
  - hypogonadal (hpg) mouse
    - lacking the gonadotropins FSH and LH mutated GnRH gene
- Gubernaculum and the cranial suspensory ligament (CSL)
  - sexually dimorphic structures
  - target tissues of androgens
- Regression of the CSL is an androgen-dependent process
  - androgens are unable to suppress CSL formation in
    - male bats with retractable testes
    - testicond mammals lacking testis descent
      - (Paenungulata,Monotremata, Edentata, Cetacea)

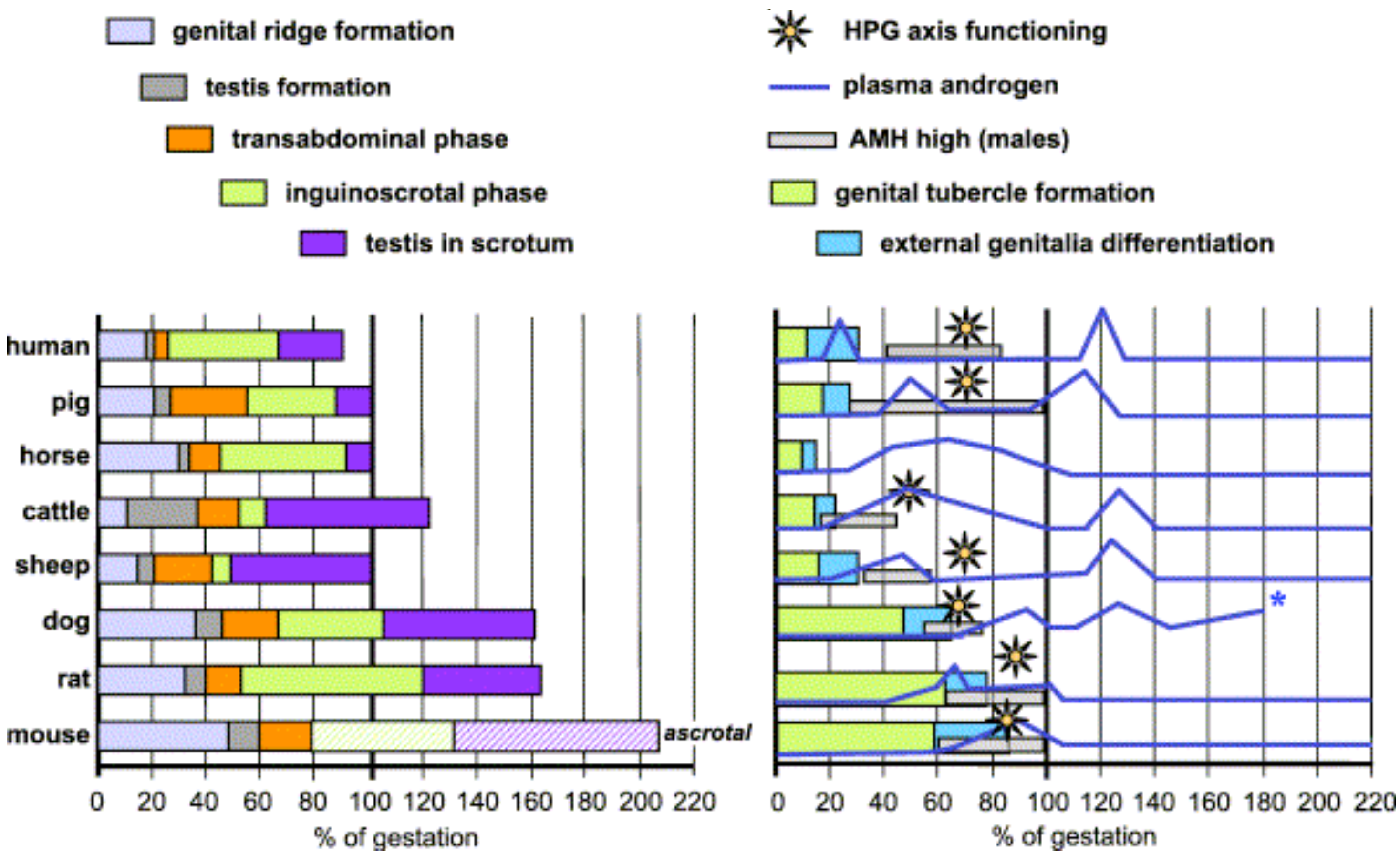
Testicular descent through the inguinal canal

- Gubernaculum
- sexually dimorphic structure
  - target tissue of androgens
- levels of AR is initially expressed independently of androgens
  - both sexes
- Then
  - increase in ligand-dependent manner in the male
  - female gubernaculum expression of AR declines
- Balance between AR and estrogen receptors (ERα and ERβ) important factor
  - Treatment of neonatal rats with DES suppresses both T levels and AR expression
- Inhibition of androgen signaling
  - by the anti-androgen flutamide
  - significant increase in ERα and ERβ

Masculinization of the Genitofemoral nerve

- Testosterone: masculinizing effects on the sensory nucleus of the genitofemoral nerve (GFN)
- In males,
  - L1 to L2 of the dorsal root ganglia
  - Unilateral transsection of the GFN causes ipsilateral cryptorchidism
- Sensory branch of the GFN acts via the neurotransmitter
  - calcitonin gene-related peptide (CGRP)
  - affects gubernacular migration during the inguinoscrotal phase.
- CGRP elicits rhythmic contractions of gubernacula
  - stimulates growth and differentiation of neonatal myogenic cells

Comparative Testis Development



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Genes - Cryptorchidism

Rodent model	Cause of cryptorchidism	Reference
DAX1$^{-/-}$ mouse	DAX1 deficiency[a]	Caron et al., 1999
Desrt$^{-/-}$ mouse	A–T rich interaction domain (ARID) class transcription factor deficiency	Lahoud et al., 2001
GnRH-promoter-driven SV40-T transgenic mouse	LHR/ FSHR deficiency	Radovick et al., 1991
GREAT$^{-/-}$ mouse	INSL3/ relaxin receptor deficiency	Overbeek et al., 2001
hpg (hypogonadal) mouse	GnRH deficiency	Charlton et al., 1983
Hoxa 10$^{-/-}$ mouse	Homeobox gene products A 10 (HOXA 10) deficiency	Satokata et al., 1995
Hoxa 11$^{-/-}$ mouse	Homeobox gene product A 11 (HOXA 11) deficiency	Hsieh-Li et al., 1995
Hoxa 10/Hoxa11	Abdominal-B-related homeobox gene product transheterozygous deficiency	Branford et al., 2000
Insl3$^{-/-}$ mouse	INSL3 deficiency	Nef and Parada, 1999; Zimmermann et al., 1999
LuRKO mouse	LHR deficiency	Zhang et al., 2001
p450AROM^{+} mouse	Aromatase overexpression[a]	Li et al., 2001
Pygmy transgenic mouse	HMGI protein(s) insertional inactivation	Zhou et al., 1995
Tfm (testicular feminization) mouse	Androgen receptor (Ar) mutations and/ or AR dysfunction[a]	Charest et al., 1991
WT1$^{-/-}$ mouse	WT1 deficiency[a]	Kreidberg et al., 1993
Trans-scrotal (TS) rat	CGRP receptor downregulation	Ikadai et al., 1988

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Summary - Ovary & Testis

Table 3. Sexually dimorphic features of the gonads.

Function	Testis	Ovary
Determining gene	SRY	Unknown
Timing of sex determination	Day 42 pc	Day 47 pc
Germ-cell status and dependence	Mitotic arrest; gonocytes not required for differentiation	Meiotic arrest; gonocytes obligatory for differentiation
Steroidogenic cell types	Leydig cells (fetal type)	Theca and granulosa cells
Steroid hormones; regulation	Androgens; hCG/LH	Androgens, progesterone, oestrogens; hCG/LH, FSH
Connective tissue/ stromal cells	Organized peritubular myoid cell layer supporting cords	Stromal cells without obvious spatial organization
Temperature dependence of gametogenesis	Scrotal temperature	Body temperature
Immune/host defence	Interstitial macrophage population	Unknown

pc, post conception; hCG, human chorionic gonadotropin; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

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