

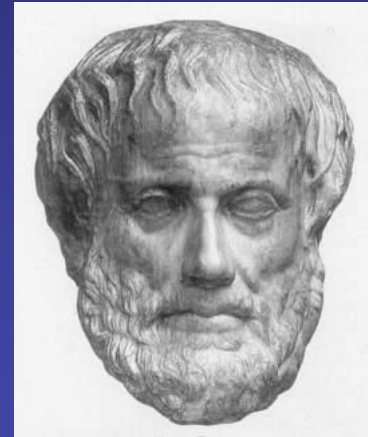
Y CHROMOSOME



X CHROMOSOME

Genetic Sex Determination

Sex is determined by the
heat of male partner during
intercourse.....



Aristotle
(384-322 B.C.)

Sex Differentiation: a favorite topic for philosophers and scientists

- | | |
|---------------------|--|
| 8th BC | Homer: Conception is influenced by the wind, north for males and south for females...at least in sheep |
| 130-200 A.D. | Galen: Semen from left testis makes females, right makes males. A mixture produces hermaphrodites. |
| 1677 | Anton van Leeuwenhoek: sperm |
| 1827 | Carl Ernst von Baer: ovum |
| 1902 | Clarence McClung: the “Accessory chromosome” |
| 1947 | Alfred Jost: differentiation of the reproductive tract |
| 1949 | Barr & Bertram: discovery of the Barr bodies |
| 1959 | Welshons & Russell: the role of the Y chromosome |
| 1991 | Lovell-Badge et al: discovery of the <i>SRY</i> gene |

The Jost Paradigm

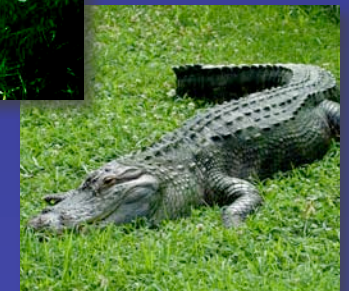
**Genetic Sex
Determination**

**Environmental Sex
Determination**

Sex Chromosomes

Switches

**Temperature,
social cues, etc**

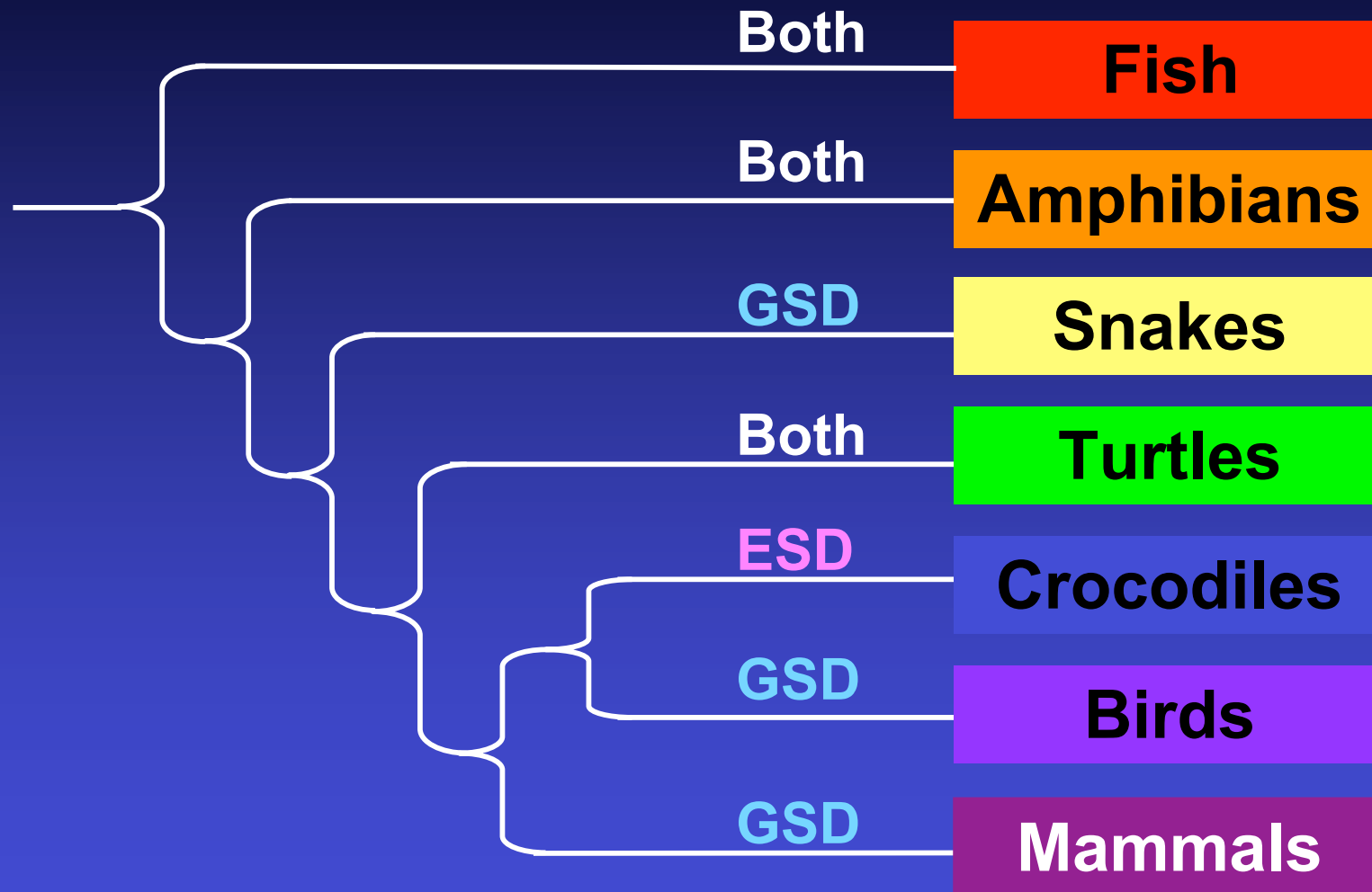


Gonadal Sex

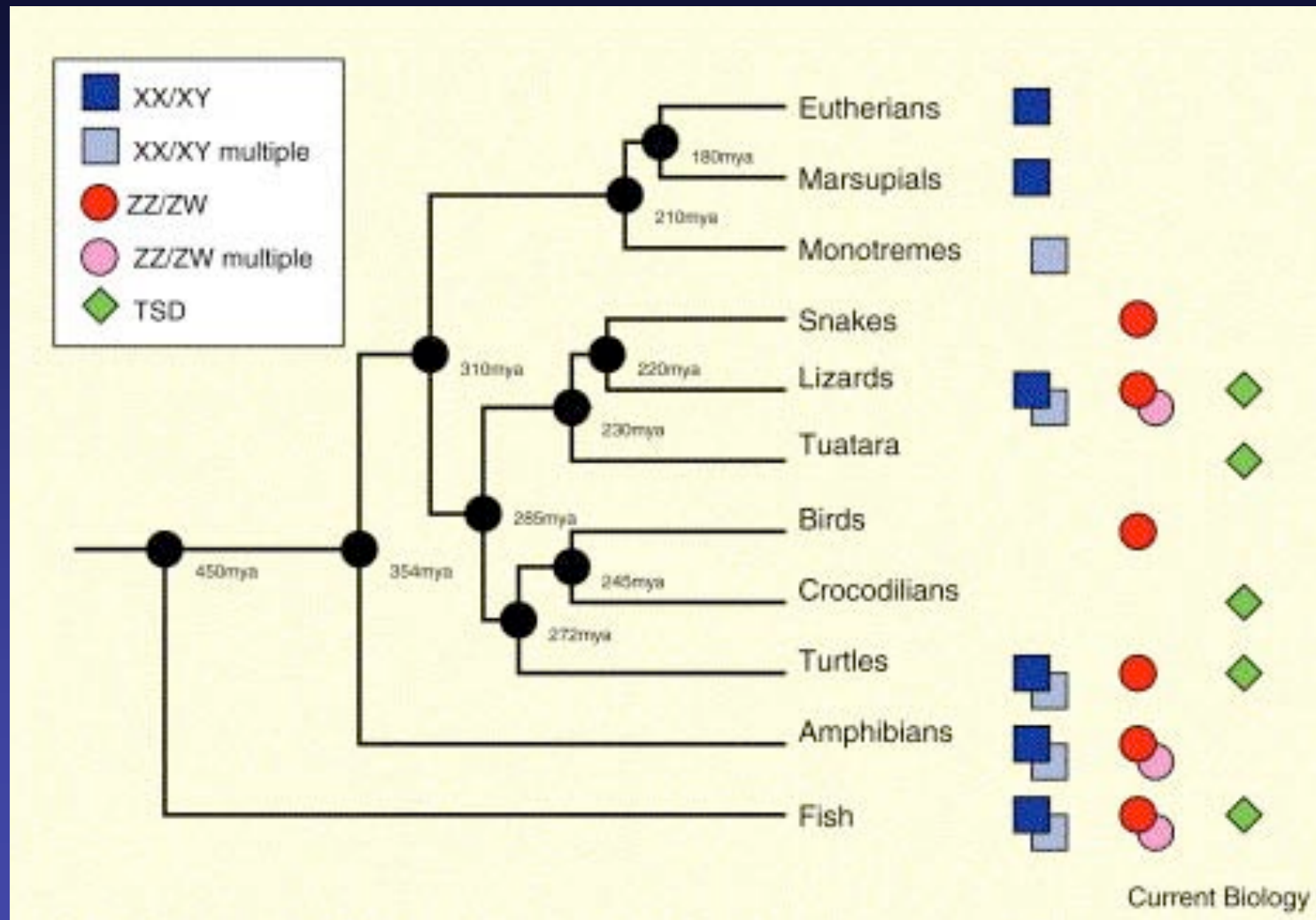
Phenotypic Sex

Courtesy of Humphrey Yao

Evolution of Sex Determination Mechanisms



Evolution of Sex Determination Mechanisms



"Preformation", or "Preformationism"

- term currently used to designate a theory of reproduction that emerged in the mid-1600
 - result of the introduction of the microscope
 - the concept
 - infinite divisibility based calculus and statistics
 - widespread belief that time for life on earth was finite
 - ranging for no more than six thousand years
 - initial theory postulated that
 - all organisms of all species, of all the generations to come, had been made by God during the six days of Creation, and had then been encased inside each other, in smaller and smaller sizes.

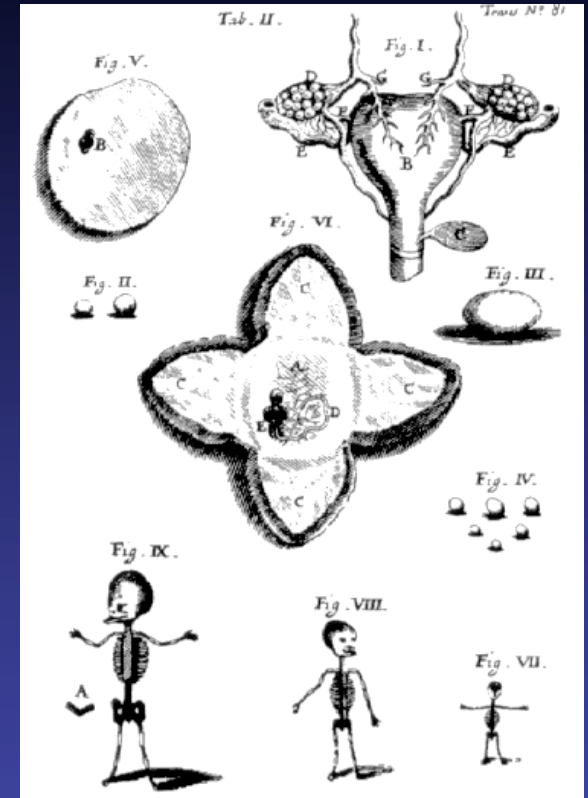


Preformationists

- split into two factions:
 - all organisms had initially been encased inside the egg (the ovists),
 - those who held that this role of mother structure had rather been ascribed to the sperm (the spermists).



Drawing of Human Spermatozoa
1694
Niklaas Hartsoeker



"little man inside the egg"
1670
Theodore Kerckring's

"The Hermit"

- Tarot card IX, "The Hermit", where "the homunculus" is represented by a reproduction of Hartsoecker's drawing of the sperm cell.

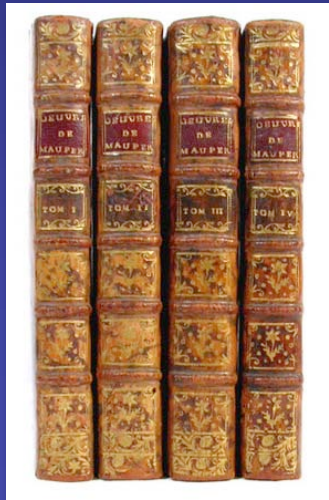


Preformationist

- In 1658, Giambattista della Porta
 - Second Book of his "Natural Magik"
 - proposed "how living Creatures of divers kinds, may be mingled and coupled together, and that from them, new, and yet profitable kinds of living Creatures may be Generated".
 - "how to generate pretty little dogs to play with"

Sex Determination

- *Earthly Venus* - offspring of different races
 - Pierre Louis Moreau de Maupertuis
 - *Venus physique / The Earthly Venus*
 - La Haye, 1745



- Speculation on organismal adaptation to environment 100 yrs before Darwin
- *Examined debate on source of humans*
 - Sperm
 - Egg
- How did he test this?
 - Hint: della Porta

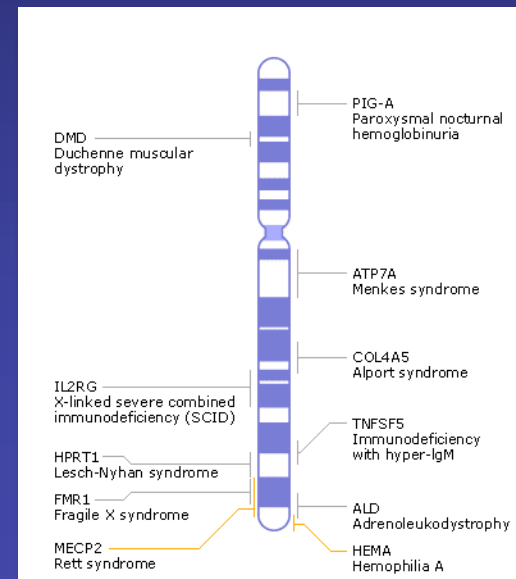
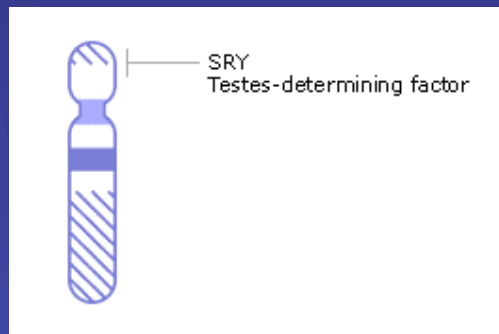
Genetics of Sex Determination

- rediscovery of Mendel /others suggested genetic factor

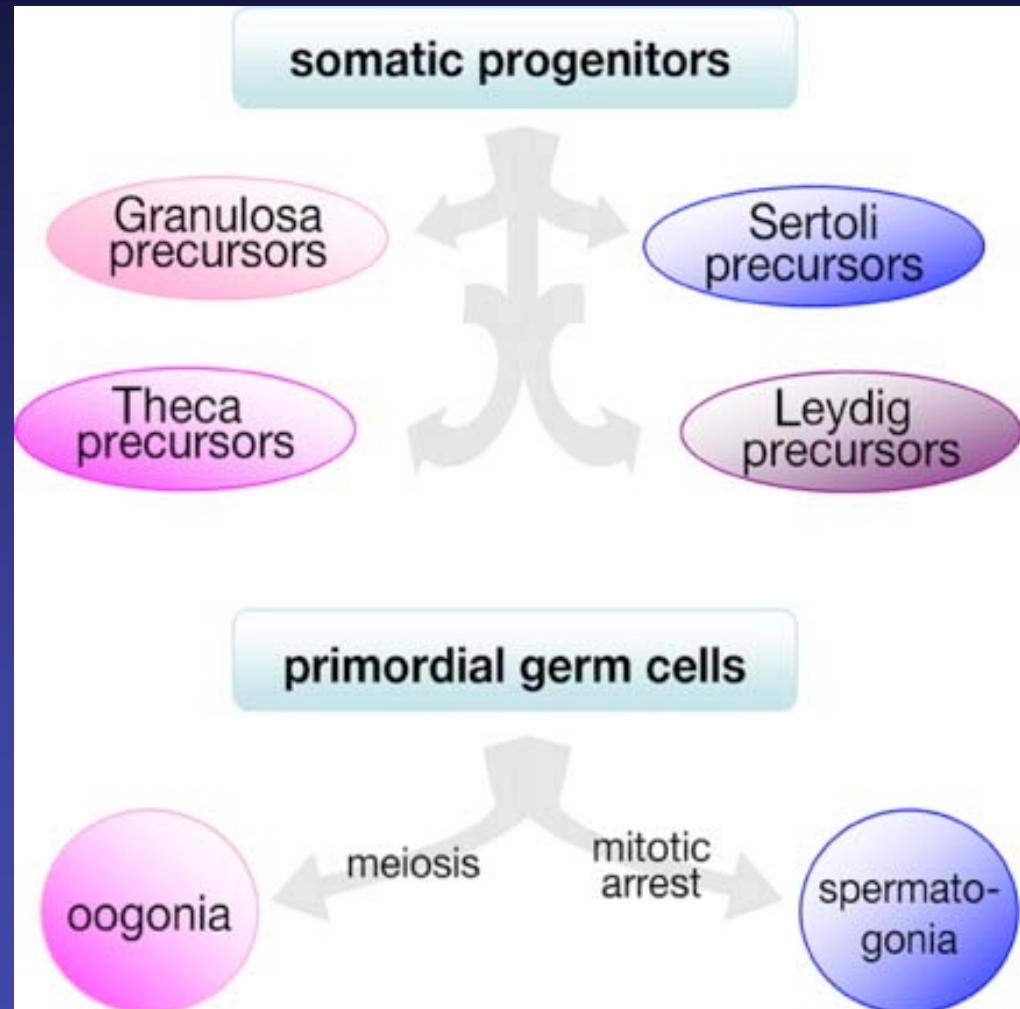
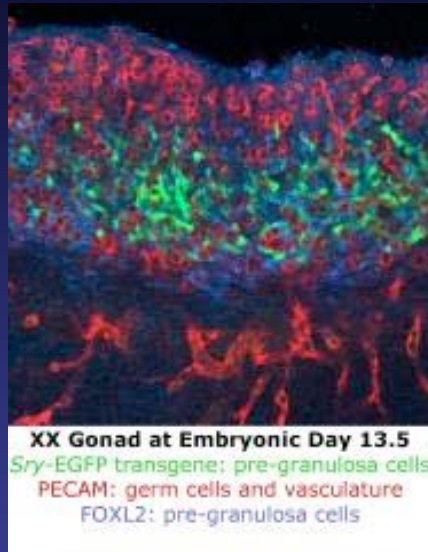
1902 Clarence McClung: the “Accessory chromosome”

1959 Welshons & Russell: the role of the Y chromosome

1991 Lovell-Badge et al: discovery of the *SRY* gene

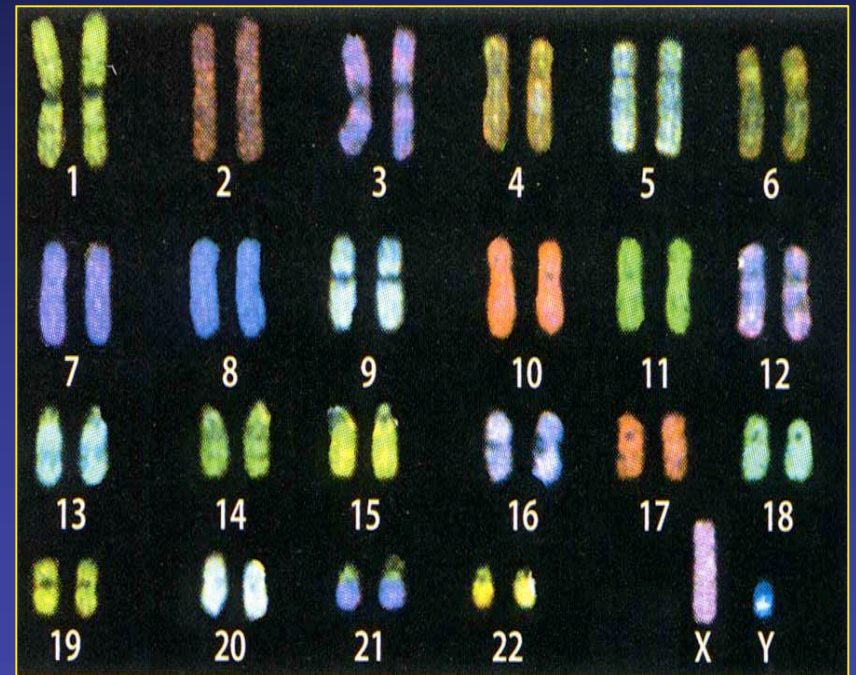


Gonadal Differentiation

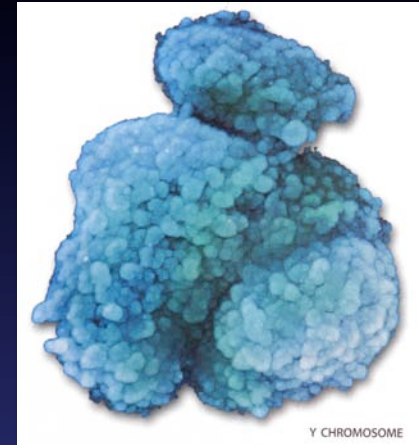


Human Primary Sex Determination

- 1. gonadal determination
- 2. chromosomal
 - a. female = XX
 - b. male = XY
- 3. number of X chromosomes not important
- 4. presence of the Y is critical

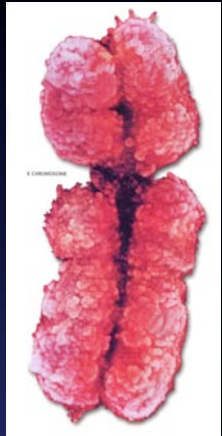


Y Chromosome



- Represents 2% of haploid complement
 - differ between species in size and gene content
 - Contains over 200 genes
 - Contains over 50 million base pairs, of which approximately 50% have been determined
- Genes for
 - Sex determination
 - Histocompatibility
 - Spermatogenesis
 - Growth
 - Cancer

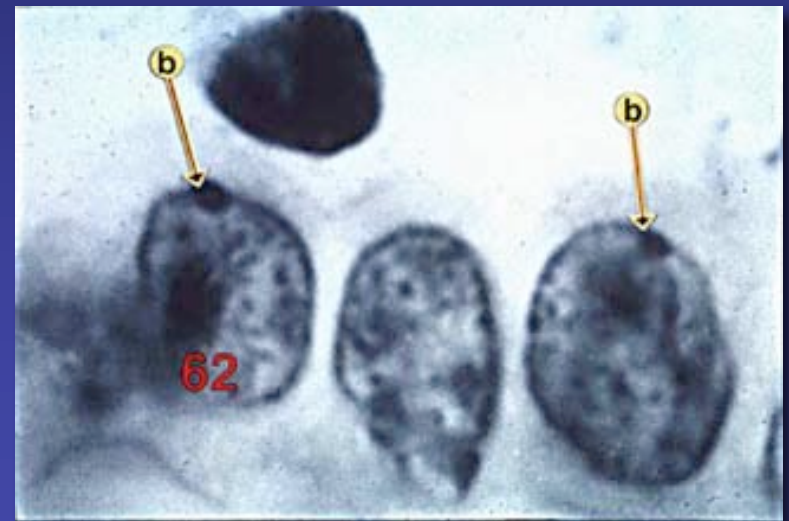
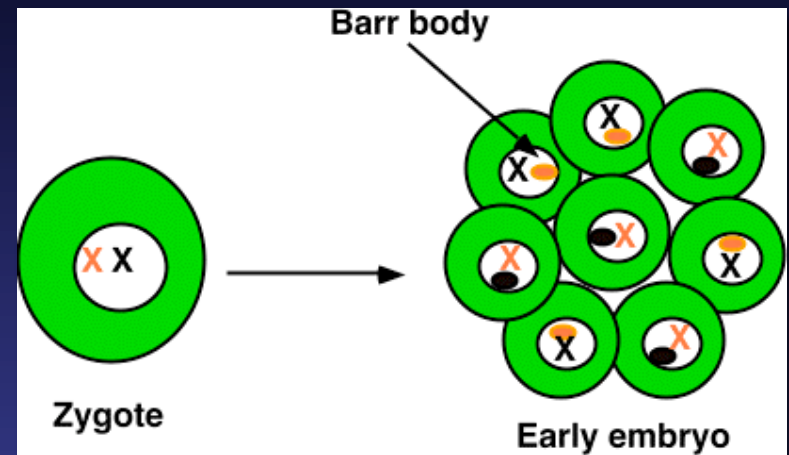
X Chromosome

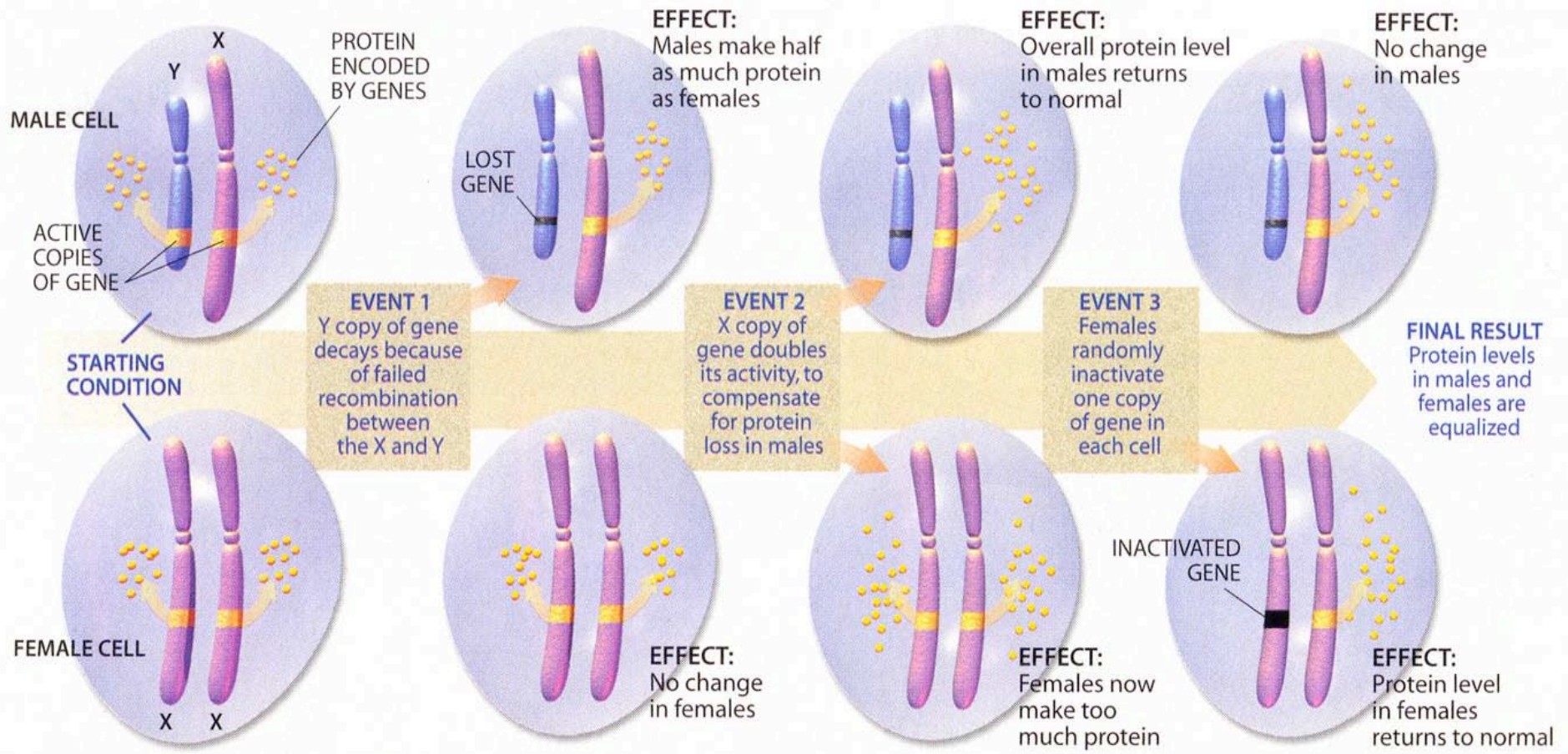


- Contains over 1400 genes
 - ~5% of the haploid genome
- Contains over 150 million base pairs
 - approximately 95% have been determined
- sex linked genes in the X chromosome
 - all these genes will be dominant
 - no opposing genes in the Y chromosome
 - freely expressed in the organisms phenotype
 - hairy ears in old age.
- Sex Linked Characteristics
 - Red-Green color blindness
 - Hemophilia - prevents the clotting of the blood
 - Hairy ears in men through advancing age

X Inactivation

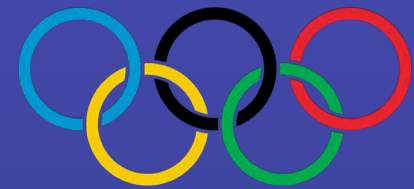
- Forms the Barr Body
- Condensation of some of the genes on one of the X chromosome
- Why?
 - Double dose of genes thus,
 - Double dose of proteins



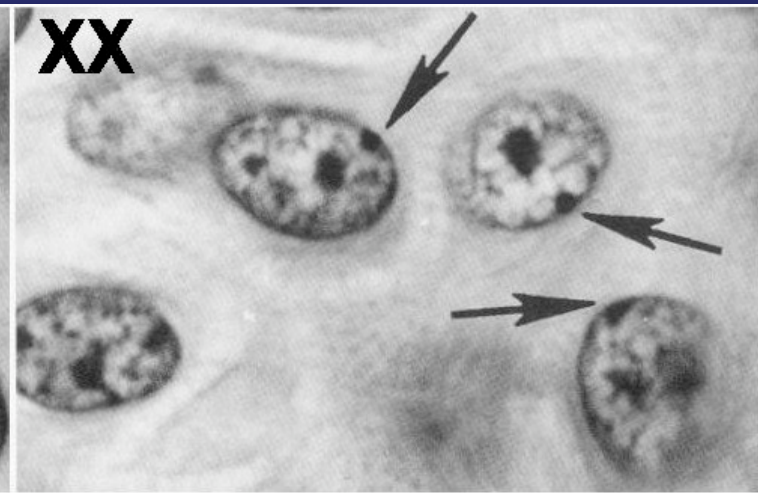


EVOLUTION OF X INACTIVATION, the silencing of most genes on one X chromosome in female cells, apparently occurred in a piecemeal fashion—one gene or a few genes at a time—to compensate for losses of genes on the Y chromosome (*diagram*). One effect of X inactivation can be seen in calico cats (*photograph*). The gene determining whether fur color is orange or black (that is, not orange) resides on the X. Females that carry the orange version on one X and the black version on the other X will end up with some orange areas and some black ones, depending on which X is shut down in each cell. A different gene accounts for the white areas.

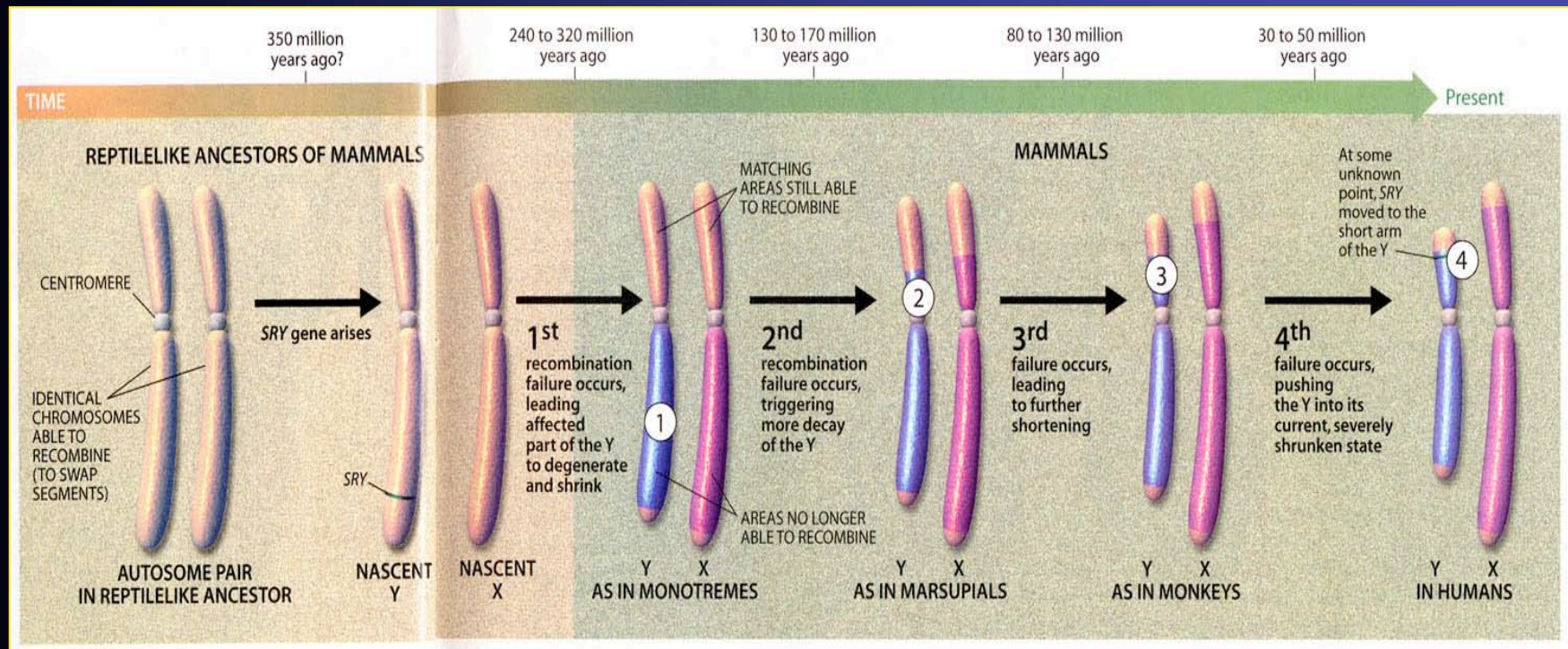
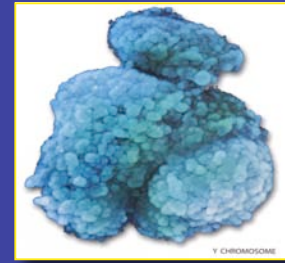
Barr body



- Mexico City Olympics - 1968
 - introduced genetic testing in the form of a sex chromatin (Barr body)
- Barcelona games
 - PCR for Y chromosome gene, SRY

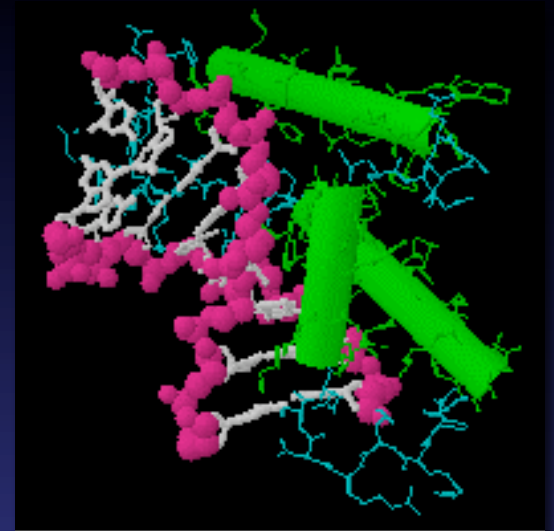


Evolution of Y Chromosome



Sex Determination

- Transcription factors critical
- Sex determination in mammals
 - Complex - multiple genes
 - SRY, DAX1, SOX9, XH2
 - WT-1 (zinc-finger protein)
 - SF-1 (steroidogenic factor -1)
 - Wnt-4
- SRY critical for testis formation

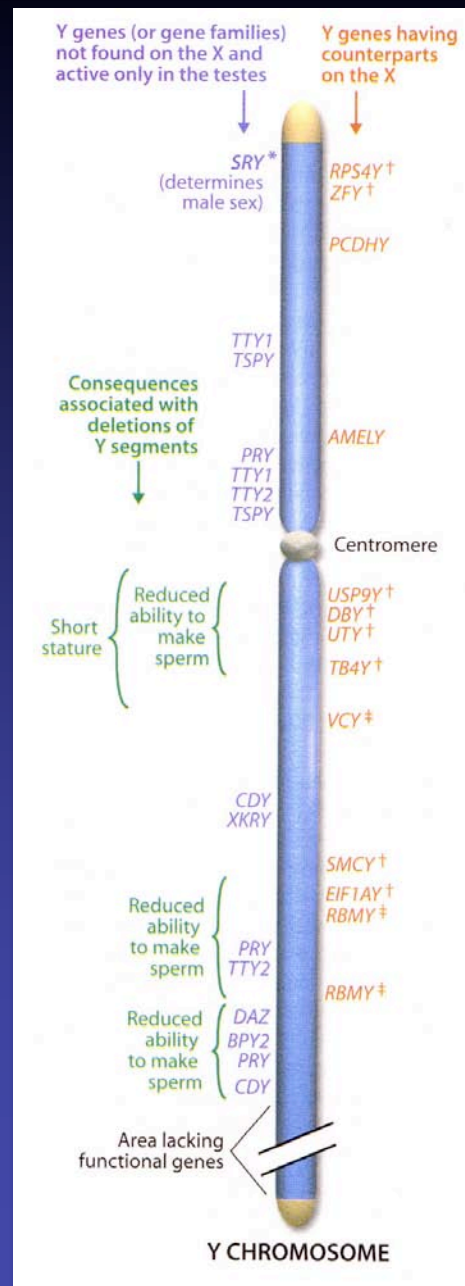


SRY (green) binds to DNA (pink) and distorts its shape. In so doing, it regulates genes that control the development of the testes.

Chronology

1. 1959: Y chromosome shown to determine males
2. 1966: Testis determining gene localized
 - short arm of Y chromosome
3. 1986-1990: XX males and XY females identified and examined
 - isolated a 35 kilobase in region 1 of Y chromosome
 - the SRY - Sex-determining Region of the Y

SRY



- A. codes for a 223 AA protein,
- B. a transcription factor
 - ligand unknown
- C. has an HMG box region, found in other transcription factors
 - 'box' binds/folds the DNA
 - essential for sex determination
 - 10-14kb genomic fragment in transgenic mice = sex reversal
 - mutation = sex reversal
- D. found in normal males and XX males (full male genotype)
- E. lacking in normal females and XY females

Evolution of Sry

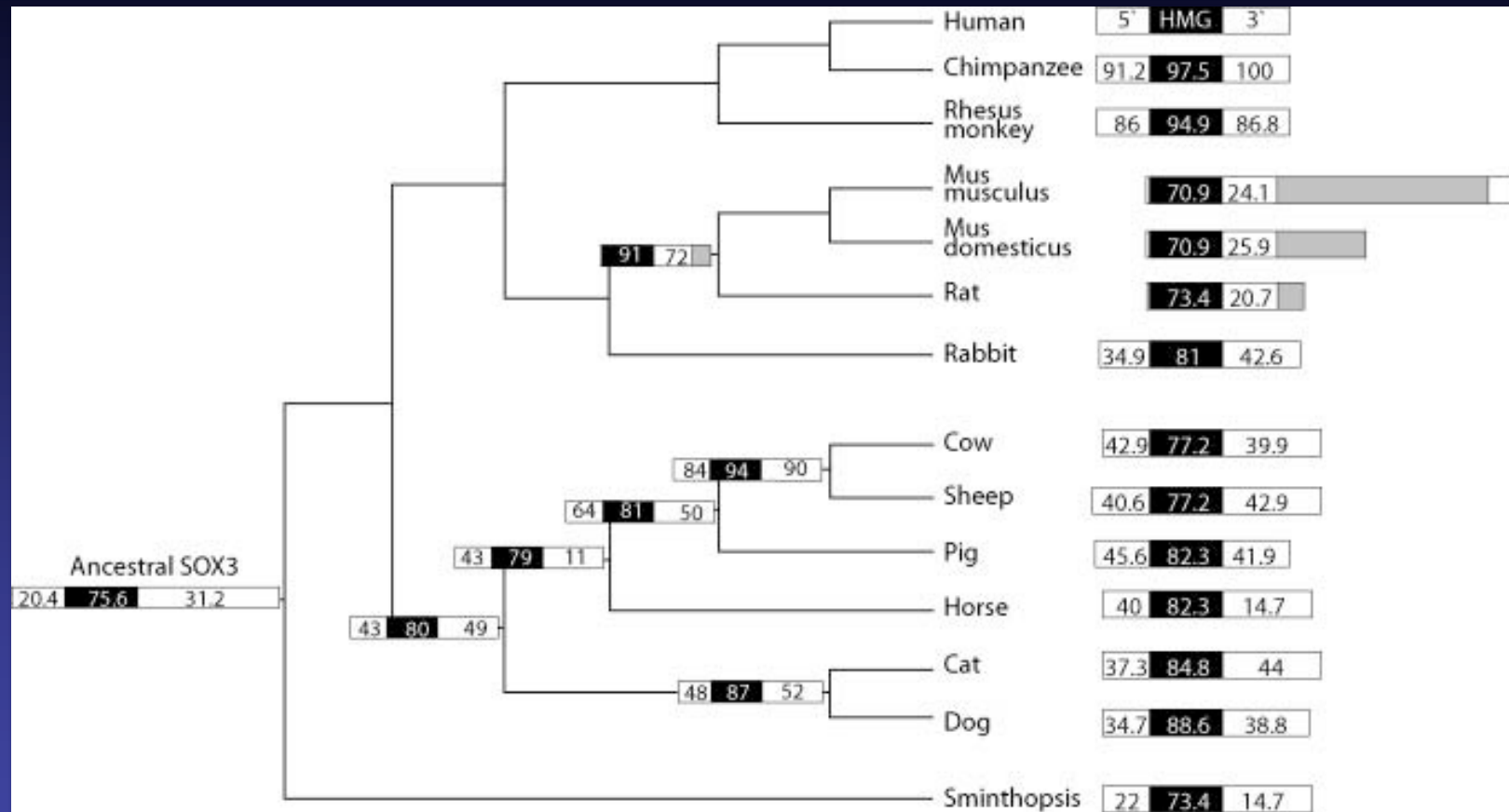


Fig. 3. Alignment of SRY polypeptide from species for which full length sequences are available on NCBI (<http://www.ncbi.nlm.nih.gov/>). The HMG box is represented in black and flanking regions in white. The glutamine rich domains of rodent *Sry* are indicated in grey. The alignment was constructed using the Clustalx algorithm (<http://www.embl.de/~chenna/clustal/darwin/index.html>). Indicated within each region of SRY that overlaps with human is the percentage of pairwise amino acid identities for all species compared to human SRY. Percent amino acid identities within clades are indicated by numbers on the branch leading to that clade. The ancestral mammalian SOX3 protein was reconstructed with a consensus sequence of human, mouse, marsupial (*Sminthopsis macroura*), chicken and *Xenopus* SOX3. The highest identities to the overlapping regions of SRY are given within the different sections of SOX3.

Sry Gene

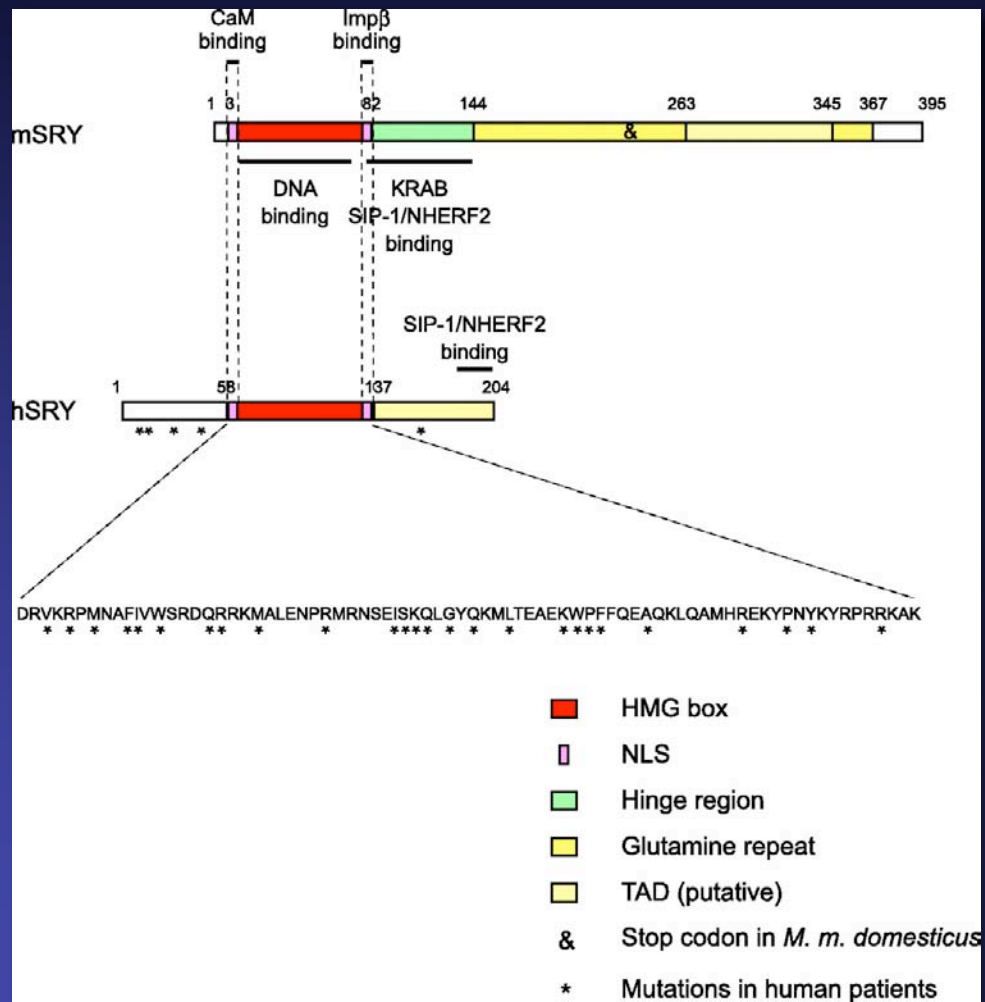


FIG. 12. Structure of mouse and human SRY protein. The HMG DNA-binding domain is shown in red and the large glutamine-rich domain of the mouse SRY COOH terminus is in dark yellow. Nuclear translocation is mediated by one NLS (pink) at either end of the HMG domain. The NH₂-terminal NLS is recognized and bound by calmodulin (CaM), whereas the COOH-terminal acts via importin β . For both mouse and human SRY, a putative transactivation domain (TAD, light yellow) has been described. The hinge or bridge region (green) interacts with mouse SRY-interacting protein 1 (SIP-1/NHERF2) and the KRAB-only protein, whereas human SRY interacts with SIP-1/NHERF2 via its COOH terminus. Sex-reversing mutations in human SRY (marked by asterisks) leading to gonadal dysgenesis or hermaphroditism are mainly found in the HMG domain.

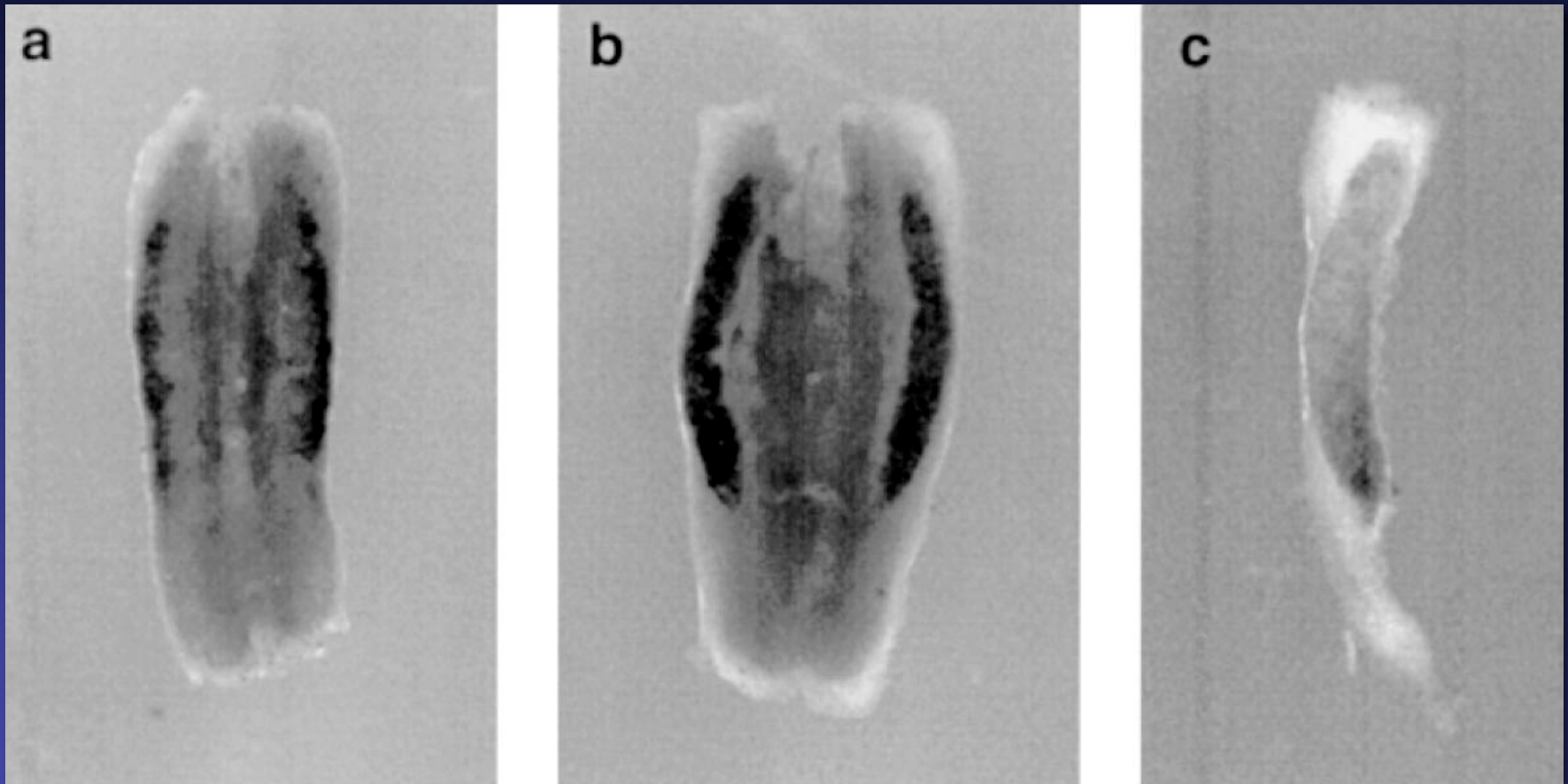
3 Functions of SRY

- 1) differentiation of Sertoli cells
- 2) induces migration of cells from the mesonephros into the genital ridges
- 3) induces proliferation of cells within the genital ridges

Mouse SRY

- ❖ homologous region
 - ❖ found in developing gonad just before testis formation (2 days prior to testis formation)
 - ❖ Also seen in the brain
 - ❖ suppressed late in development

Mouse testis formation - in situ whole mount for SRY



Day 14

Day 20

Day 26

Mouse SRY

- ❖ inject SRY into XX mouse embryo
 - ❖ some develop testis, ducts and penis
 - ❖ Gene dosing very important
 - ❖ no spermatogenesis - normal for XXY males
 - ❖ another gene ZFY associated with germ cells
- ❖ SRY works with other genes
 - ❖ alone does not always give testis
- ❖ SRY probably stimulates/blocks a number of genes

TABLE 1. *Genes implicated in sexual development in mammals*

Gene	Protein Function	Gonad Phenotype of Null Mice	Human Syndrome	Reference Nos.
<i>Bipotential gonad</i>				
<i>Wt1</i>	Transcription factor	Blockage in genital ridge development	Denys-Drash, WAGR, Frasier syndrome	71, 134
<i>Sf1</i>	Nuclear receptor	Blockage in genital ridge development	Embryonic testicular regression syndrome	143, 200, 214
<i>Lhx9</i>	Transcription factor	Blockage in genital ridge development	*	20
<i>Emx2</i>	Transcription factor	Blockage in genital ridge development	*	158
<i>M33</i>	Transcription factor	Gonadal dysgenesis	*	120
<i>Testis-determining pathway</i>				
<i>Gata4/ Fog2</i>	Transcription/cofactor	Reduced <i>Sry</i> levels, XY sex reversal	*	227
<i>Sry</i>	Transcription factor	XY sex reversal	XY sex reversal (LOF); XX sex reversal (GOF)	19, 132
<i>Sox9</i>	Transcription factor	XY sex reversal	Campomelic dysplasia, XX sex reversal (GOF)	10, 21, 48, 76, 230, 241, 242
<i>Sox8</i>	Transcription factor	XY sex reversal in combination with partial loss of <i>Sox9</i> function	*	48
<i>Fgf9</i>	Signaling molecule	XY sex reversal	*	51, 206
<i>Dax1</i>	Nuclear receptor	Impaired testis cord formation and spermatogenesis	Hypogonadism	26, 153, 154, 163
<i>Pod1</i>	Transcription factor	XY sex reversal	*	54
<i>Dhh</i>	Signaling molecule	Impaired differentiation of Leydig and PM cells	XY gonadal dysgenesis	23, 43, 44, 49, 189, 237
<i>Pgdra</i>	Receptor	Reduction in mesonephric cell migration	*	31
<i>Pgds</i>	Enzyme	No phenotype	*	1, 145, 245
<i>Arx</i>	Transcription factor	Abnormal testicular differentiation	X-linked lissencephaly with abnormal genitalia	118, 127
<i>Atrx</i>	Helicase	ND	ATRX syndrome	226
<i>Instl3</i>	Signaling factor	Blockage of testicular descent	Cryptorchidism	2, 115, 168, 261
<i>Lgr8</i>	Receptor	Blockage of testicular descent	Cryptorchidism	2, 72, 115
<i>Hoxa10</i>	Transcription factor	Blockage of testicular descent	Cryptorchidism	97, 102
<i>Hoxa11</i>	Transcription factor	Blockage of testicular descent	Cryptorchidism	97, 102
<i>Amh</i>	Hormone	No Müllerian duct degeneration	Persistent Müllerian duct syndrome	14, 15, 100
<i>Misrl1</i>	Receptor	No Müllerian duct degeneration	Persistent Müllerian duct syndrome	94, 100
<i>Pax2</i>	Transcription factor	Dysgenesis of mesonephric tubules	*	45
<i>Lim1</i>	Transcription factor	Agenesis of Wolffian and Müllerian ducts	*	128, 129
<i>Dmrt1</i>	Transcription factor	Loss of Sertoli and germ cells	XY female†	194
<i>Ovary-determining pathway</i>				
<i>Wnt4</i>	Signaling molecule	Müllerian duct agenesis, testosterone synthesis, and coelomic vessel formation	XY female (GOF)	89, 239
<i>FoxL2</i>	Transcription factor	Premature ovarian failure	BPES	53, 175, 207, 236
<i>Dax1</i>	Nuclear receptor	XY sex reversal (GOF)	XY sex reversal (GOF)	110, 163, 223, 257

SOX9

- codes for a transcription factor
 - Protein activates genes in male sex pathway
 - Usually 1 copy of SOX9
- missing copy = COMPOMELIC DYSPLASIA
 - die soon after birth from respiratory distress,
 - Skeletal abnormalities
 - SOX9 induces collagen II gene expression
 - But...75% of XY individuals lacking SOX9 develop as female or hermaphrodites

SOX 9 and Testis

- SOX9 essential for normal testis formation
 - SOX9 only expressed in males on genital ridge
 - co-localized in cells with SRY gene expression
 - not in females

Sry/Sox9/PGs Sertoli Cell Recruitment

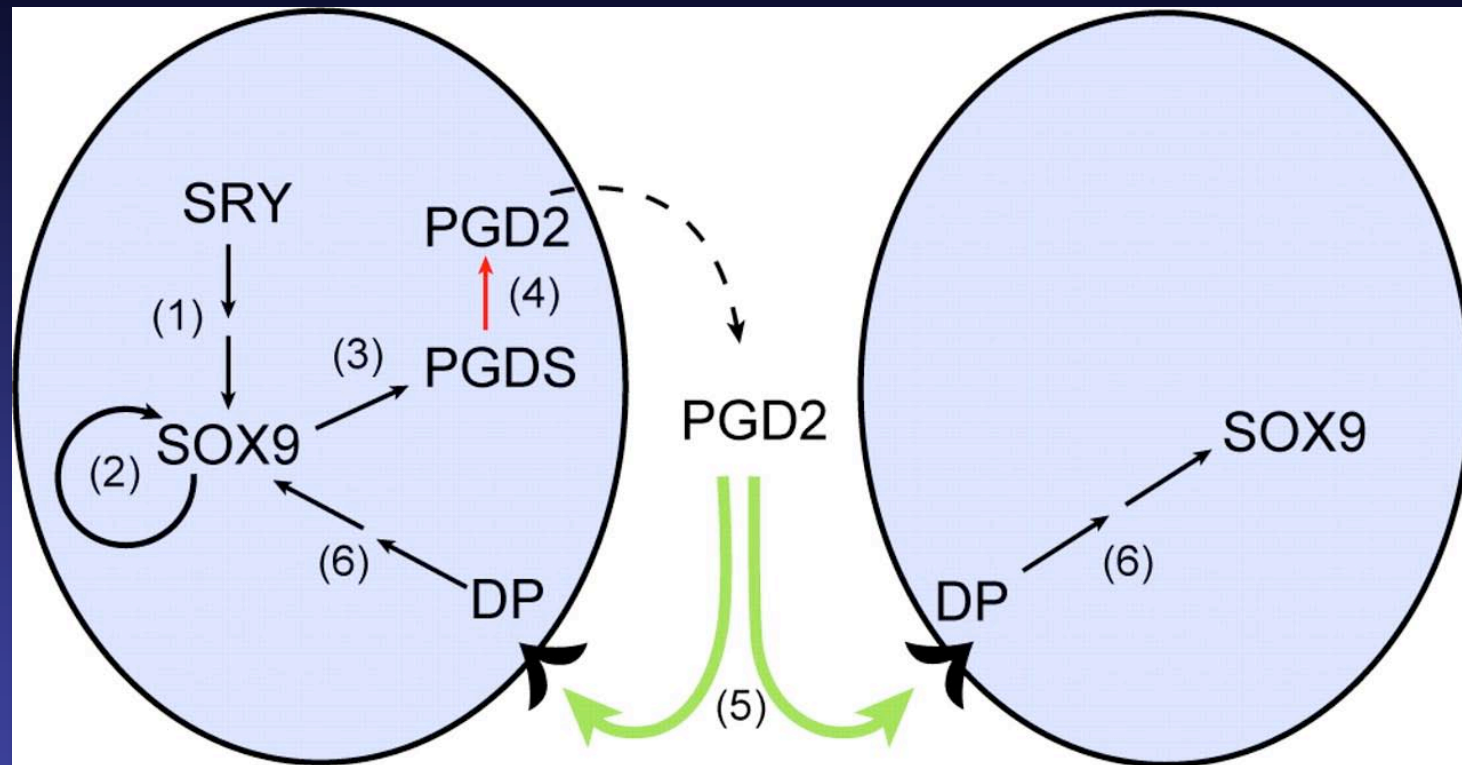


FIG. 8. Model for cell-autonomous and prostaglandin-mediated up-regulation of *Sox9* in pre-Sertoli cells. *Sry* induces *Sox9* cell-autonomously either via a direct or indirect regulatory mechanism (1). Subsequently, *Sox9* maintains its own expression in an autoregulatory loop (2). In addition, *Sry* and/or *Sox9* serve to upregulate *Pgds* (3), which leads to prostaglandin D₂ (PGD₂) synthesis (4) and secretion. PGD₂ can act by binding to its receptor DP (5), to upregulate *Sox9* expression in a paracrine, and possibly also an autocrine manner (6). Thus cells that do not express *Sry* or fail to reach a threshold of *Sry* expression can be induced to upregulate *Sox9* and differentiate as Sertoli cells. [Adapted from Smith et al. (216).]

SF-1 - Orphan Receptor

- a. cofactor with SRY
- b. transcription factor coded for on an autosomal gene
- c. activates genes coding for androgen synthesis
- d. SF-1 present in genital ridge for testis formation, decreases with ovarian development
 - persistence activates
 - MIH in Sertoli cell
 - androgens in Leydig cell
 - Works together with SRY

SF-1 mutation

- lack of SF-1
 - mouse = no gonads or adrenal
 - gonads develop then die
 - animals die due to lack of corticosterone

DMRT-1

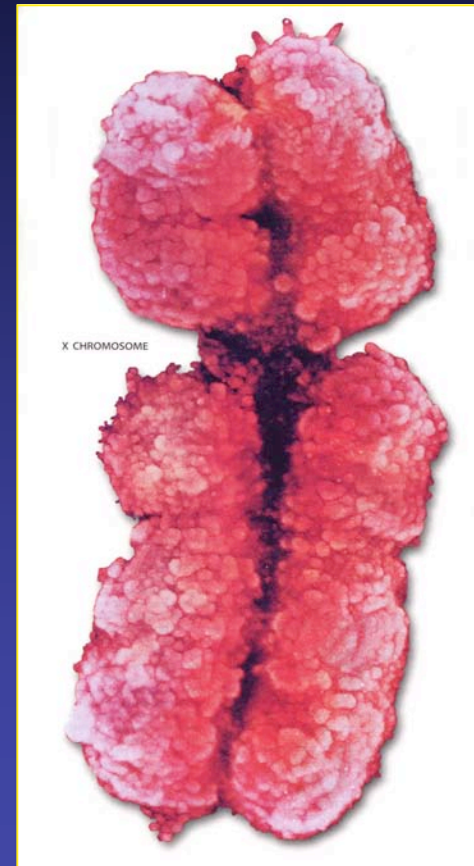
- DM-related Transcription factor
 - Putative sex determining gene in mammal
 - Related to genes determining males in *Drosophila*
 - Has DNA binding region - DM domain
 - Missing in humans = XY female
 - Expressed in male embryo only (testis)

Other Genes

- XH2
 - X chromosome located
 - helicase family - codes for H type hemoglobin
 - Mutation gives
 - Female phenotype with 46 XY genotype
- DMRT-1
 - Expressed only in male genital ridge
 - Deletion in humans = female phenotype
 - Ortholog DMRT-2 may also be involved
- WT-1
 - Wilms tumor 1 gene
 - Missing/mutation = undifferentiated gonad

Ovarian Development

- Considered default in mammals
- Still requires genetic pathway
- Formed with lack of Y
 - Usually two 'X' chromosomes



Ovarian Development- DAX 1

- 1. potential ovary determining gene
- 2. two sisters - "normal XY" - "Y" was normal
 - duplicated region on the small arm of X (Xp21)
 - two copies - reversed the SRY gene activation
- 3. normal testis formation would override this factor with normal number of DAX1 copies
- 4. codes for a member of nuclear hormone receptor family - gene transcription factors
- 5. Orphan Receptor - ligand unknown
- 6. localized gene activity on the genital ridge

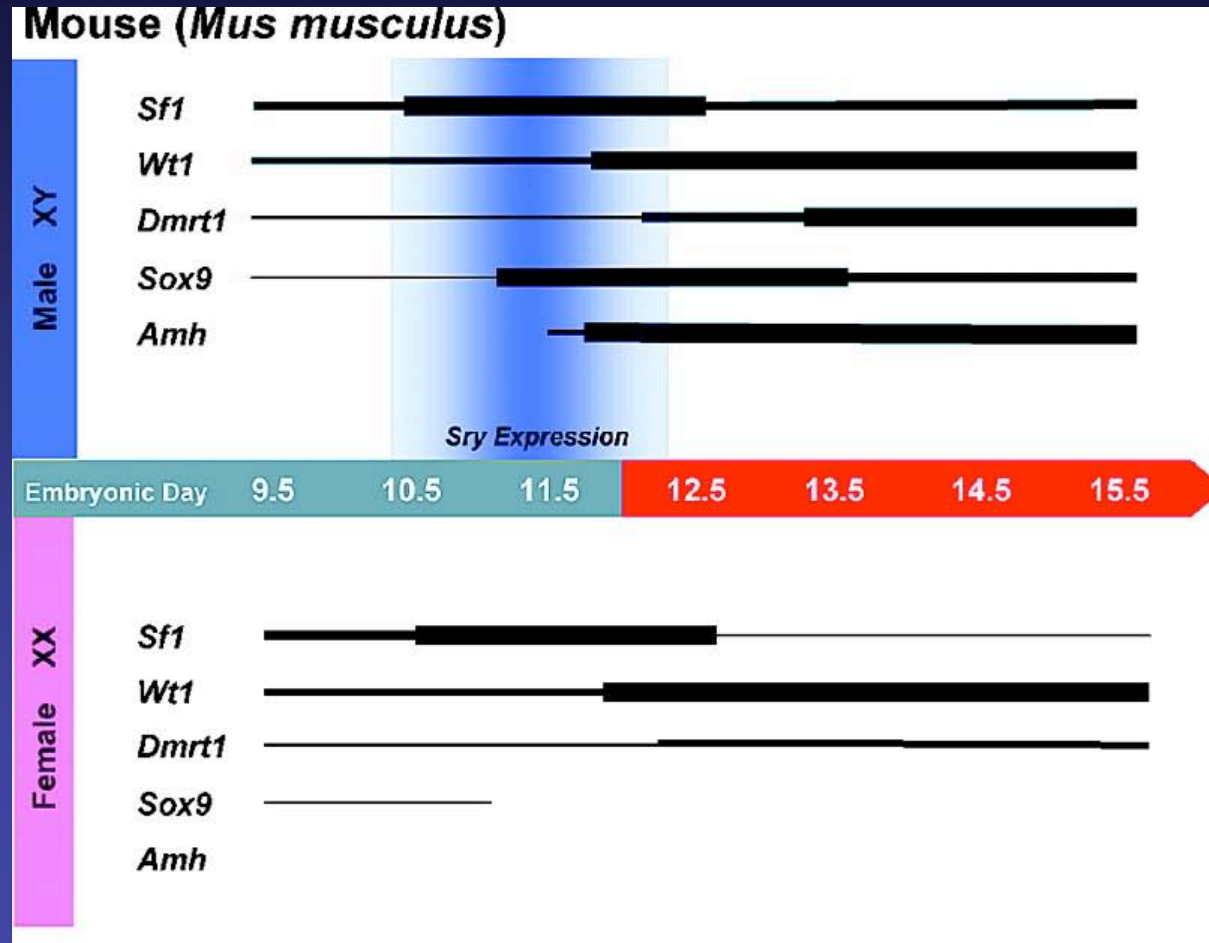
Wnt-4

- 1. Localized gene activity
 - on the genital ridge of mouse
- 2. Expressed in undifferentiated gonad
 - disappears with XY testis formation
 - Absence does not influence testis formation
- 3. with XX genotype
 - ovary forms and Wnt-4 expressed

Missing Wnt-4

- Missing Wnt-4
 - partial female -> male reversal
 - mutant ovary forms
 - Secrete testosterone and AMH (MIH)
 - 3β -HSD and 17α -hydroxylase detected
 - Number of oocytes dramatically reduced
- Similar mutant ovaries seen in $\alpha\beta$ ERKO mice
 - suggested that ER may control Wnt-4
- SRY may repress Wnt4a and activate SF1

Mouse Sex Determination



Fgf9 / Wnt4 Signals

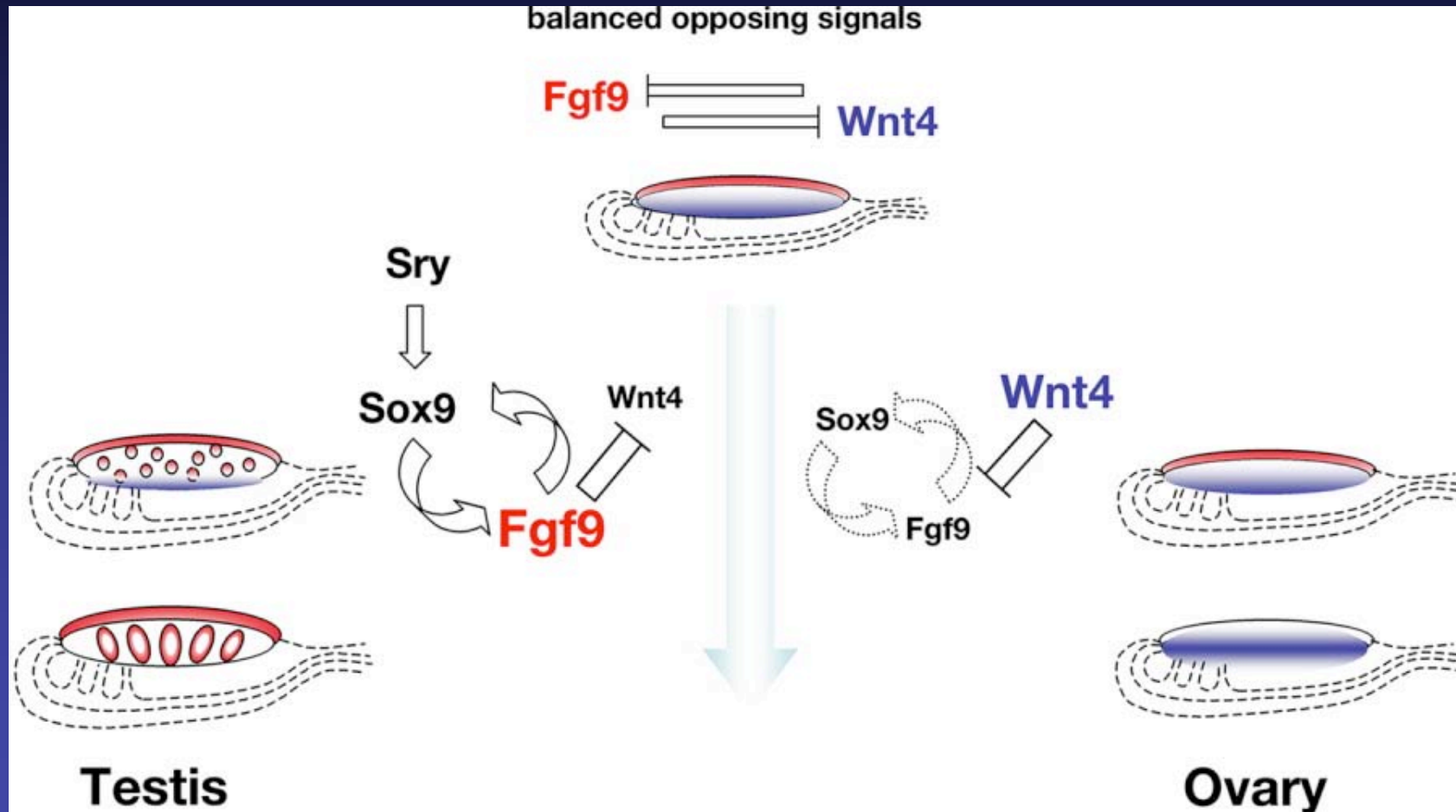


Fig. 3. Model of balanced opposing signals between *Fgf9* and *Wnt4*. In XY gonads, *Sry* upregulates *Sox9* to establish a feed-forward loop that upregulates *Fgf9* and silences *Wnt4*. In XX gonads, *Wnt4* dominates and silences *Fgf9* and *Sox9*.

Proposed Gene Interactions - Testis Differentiation

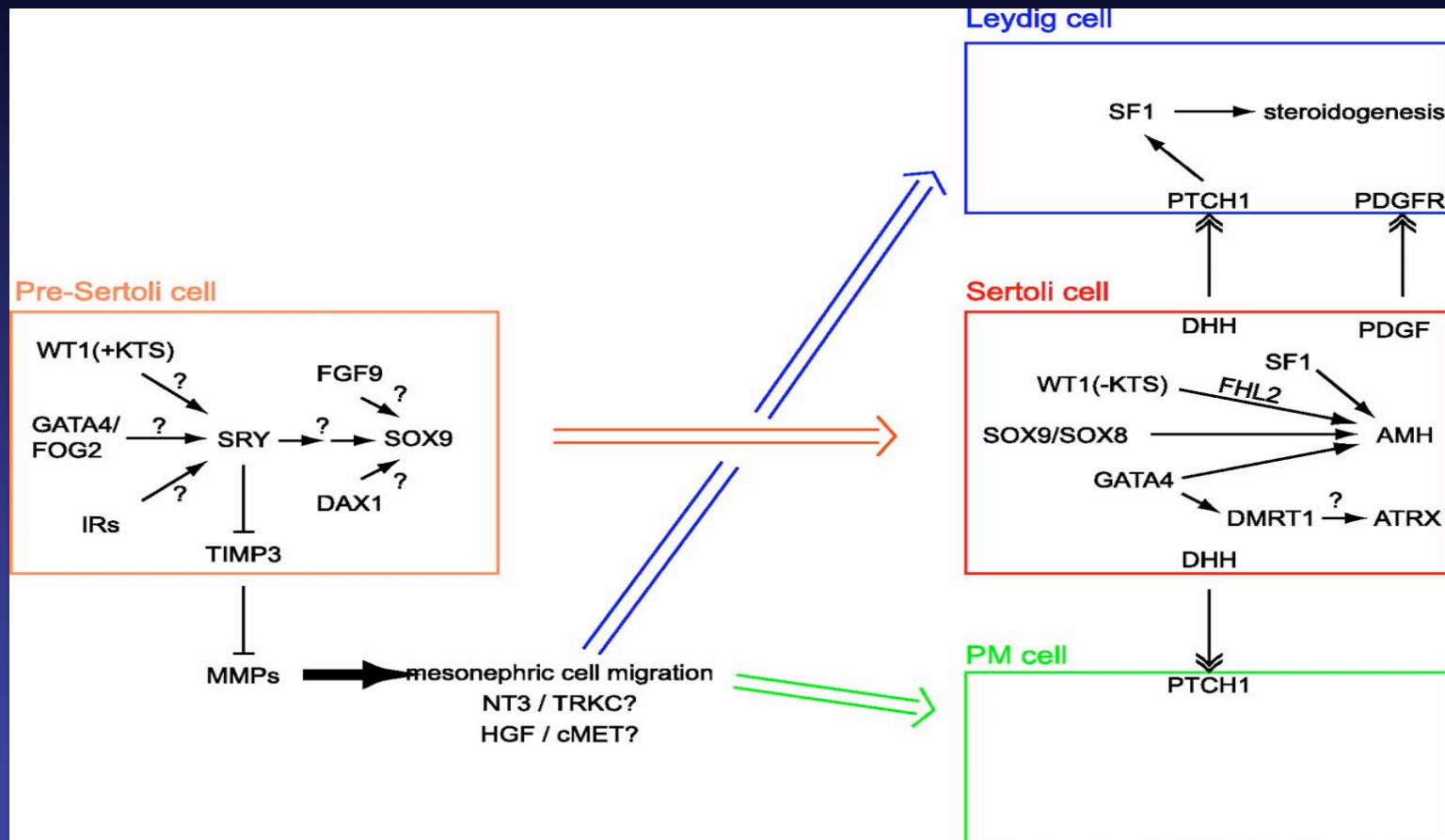
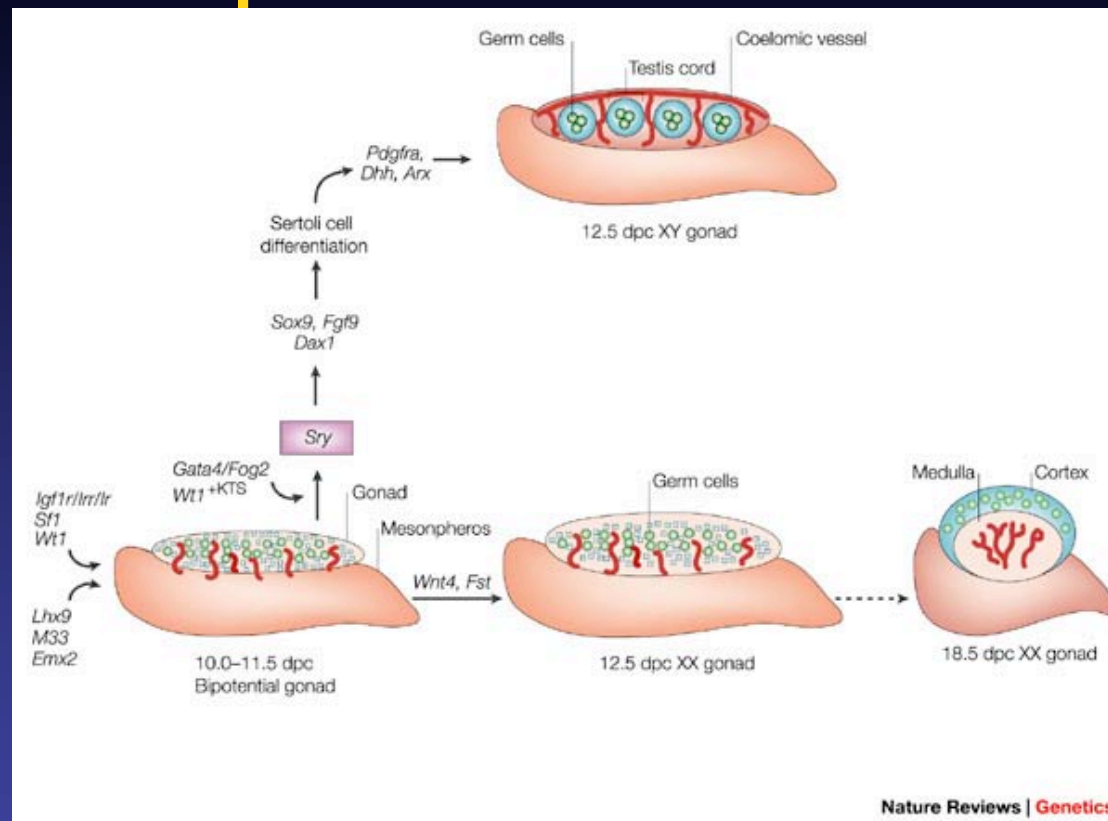


FIG. 13. Postulated interaction of molecular players involved in early testicular development. See text for details. Double-headed arrows, binding to a receptor; colored arrows (blue, red, green), differentiation of precursor cells into testis-specific cell types; black, bold arrow, gene important for cellular process.

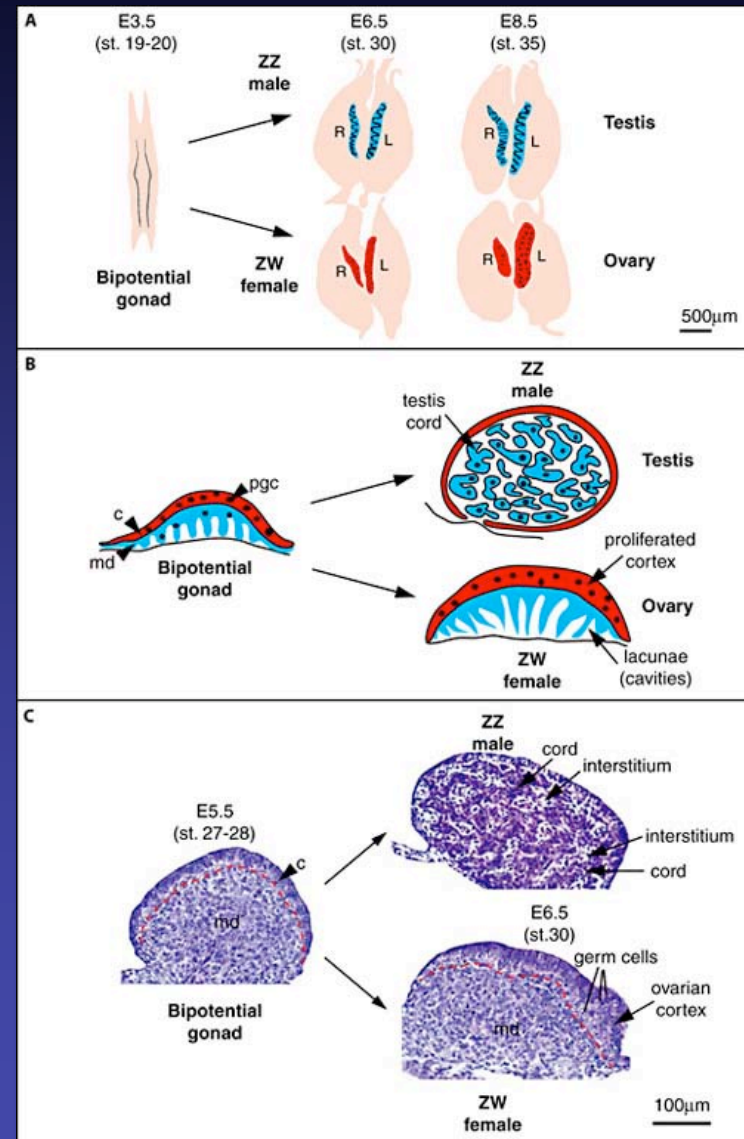
Bipotential Gonad



- Several factors are required between 10.5–11.5 days post coitum (dpc) for the outgrowth of the early bipotential gonad by preventing apoptosis or promoting cell proliferation (*Sf1*, *Wt1*, *Lhx9*, *M33*, *Emx2*, *Igf1r/Irr/Irr*). Between 10.5–12.0 dpc, *GATA4/FOG2* and *WT1+KTS* are implicated in the activation of *Sry* expression in the XY gonad. *Sry* expression diverts the XY gonad towards the testis fate. *Sox9*, *Fgf9* and *Dax1* are implicated in the early steps of the male pathway after the initiation of *Sry* expression. Downstream signalling pathways promote the rapid structural changes that characterize early testis development (*Pdgf*, *Dhh*, *Arx*). By contrast, few morphological changes are apparent in the XX gonad until near birth (18.5 dpc), when ovarian follicles begin to form in the ovarian cortex. *Wnt4* and *Fst* are the only two genes with characterized functions in early ovarian development. *Arx*, aristaless related homeobox; *Dax1*, nuclear receptor subfamily 0, B1 (*Nr0b1*); *Dhh*, desert hedgehog; *Emx2*, empty spiracles homologue 2; *Fgf9*, fibroblast growth factor 9; *Fog2*, zinc finger protein, multitype 2 (*Zfp2*); *Fst*, follistatin; *Gata4*, GATA binding protein 4; *Igf1r*, insulin-like growth factor 1 receptor; *Ir*, insulin receptor; *Irr*, insulin receptor-related receptor; *Lhx9*, LIM homeobox protein 9; *M33*, chromobox homologue 2 (*Cbx2*); *Pdgf*, platelet-derived growth factor; *Sf1*, nuclear receptor subfamily 5, group A member 1 (*Nr5a1*); *Sox9*, Sry-like HMG-box protein 9; *Wnt4*, wingless-related MMTV integration site 4; *Wt1*, Wilms tumour homologue.

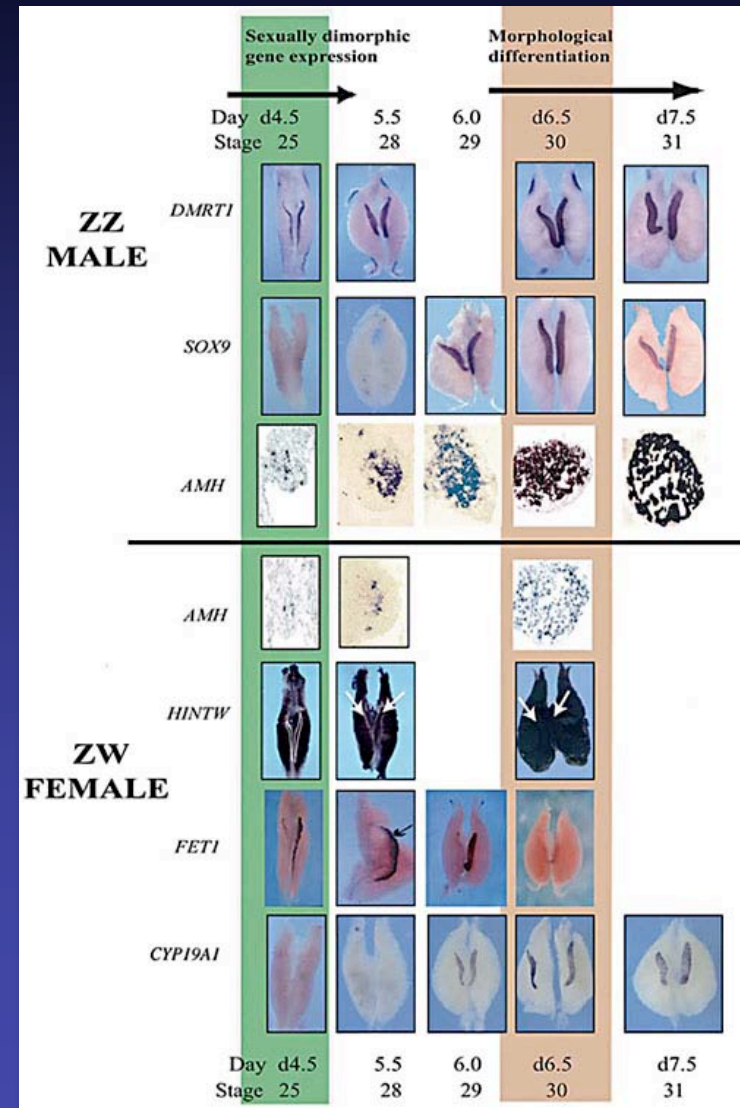
Bipotential Gonad

Fig. 1. Gonadal development and sexual differentiation in the chicken embryo. **(A)** Schematic of gonadal anatomy. At embryonic day 3.5 (stage 19–20), the gonads are undifferentiated or bipotential (shown in blue), on the medial surface of the mesonephric kidneys (pale brown). In ZZ males, bilateral testes develop, while, in ZW females, the left gonad becomes an ovary and the right regresses. **(B)** Schematic of gonadal histology. The bipotential gonad comprises an outer cortical layer (c), and underlying medulla (md). Primordial germ cells (pgc) are concentrated mainly in the cortex. Testis formation involves the condensation of medullary cords into seminiferous (testis) cords. The (left) ovary is characterised by cortical proliferation, while the medulla becomes reticulated, with numerous cavities (lacunae). **(C)** Gonadal histology in the chicken embryo. At embryonic day 5.5 (E5.5; stage 27–28) the gonads are histologically undifferentiated. The cortex (c) is distinct from the underlying medulla (md). In ZZ males, condensing cords are apparent by E6.5 (stage 30). The interstitium (site of Leydig cell development and testosterone synthesis) is present between the cords. In contrast, cortex proliferation, including germ cell proliferation, is apparent in ZW females.



Chicken Gonad Differentiation

Fig. 2. Timing of gene expression in embryonic chicken gonads, as assessed by whole mount and tissue section in situ hybridisation. The onset of morphological differentiation into testes or ovaries is shown (from day 6.5; stage 30). In ZZ males, *DMRT1* mRNA expression is detectable from day 3.5–4.5 (stages 20–25). In comparison, *SOX9* in males is first detectable at day 6.0 (stage 29). In ZW females, *HINTW* mRNA is expressed from days 3.5–4.5 (stages 20–25). *FET1* mRNA is also expressed from days 3.5–4.5, but asymmetrically expressed, with stronger expression in the left gonad. *FET1* expression is down-regulated in the gonads by day 6.5 (stage 30). In comparison, *CYP19A1* is first detectable at day 6.0 (stage 29). *AMH* is first detectable at stage 25 in both sexes, but appears higher in males, according to tissue section in situ hybridisation. By stage 28, this dimorphism in *AMH* is clear (left gonads only are shown). The onset of *AMH* expression precedes *SOX9* expression in males, and *CYP19A1* expression in females. The *AMH* expression is taken from Oreal et al. (1998) with permission.



Bipotential Duct System

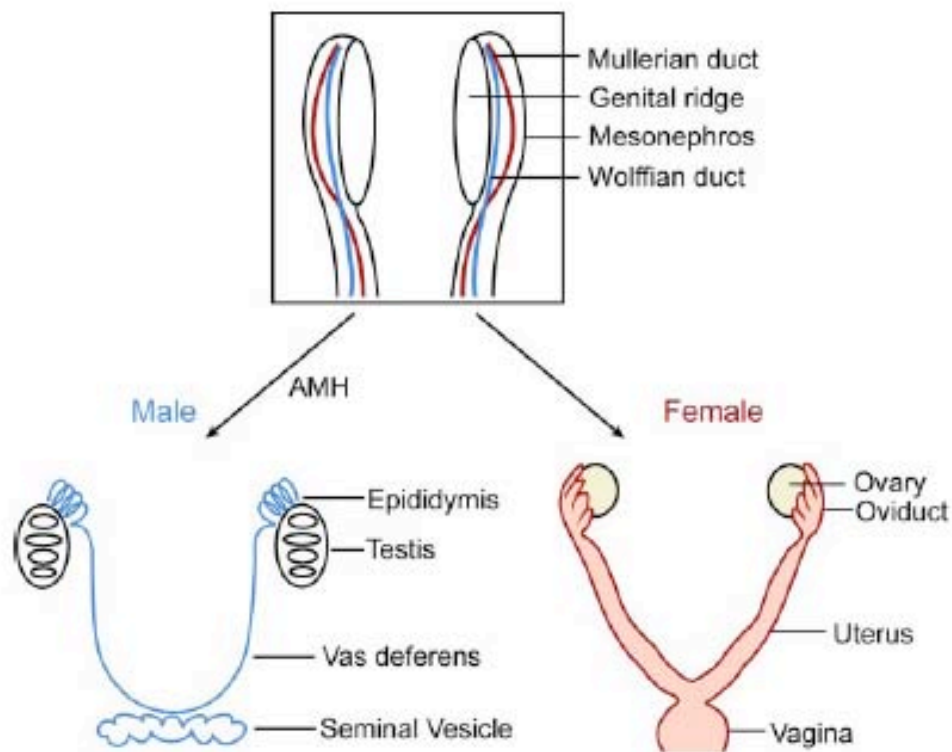


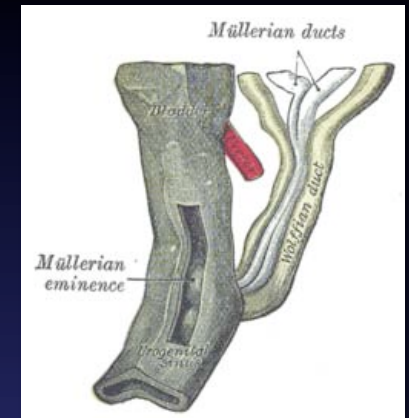
FIG. 4. Development and differentiation of the genital duct system. Both Müllerian and Wolffian ducts are present at the bipotential stage. In males, the Müllerian ducts degenerate under the influence of AMH secreted by the testicular Sertoli cells, whereas the Wolffian ducts differentiate into epididymides, vasa deferentia, and seminal vesicles under the control of androgens produced by Leydig cells. In females, the Wolffian duct regresses and the Müllerian duct differentiates into oviduct, uterus, and upper vagina.

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Duct/Genitalia Development

- Hormonal Regulation
- a. MIH (Müllerian Inhibiting Hormone) - Müllerian duct
- b. Androgens
 - 1. ducts - testosterone
 - 2. penis/prostate - dihydrotestosterone

Mullerian Duct Formation

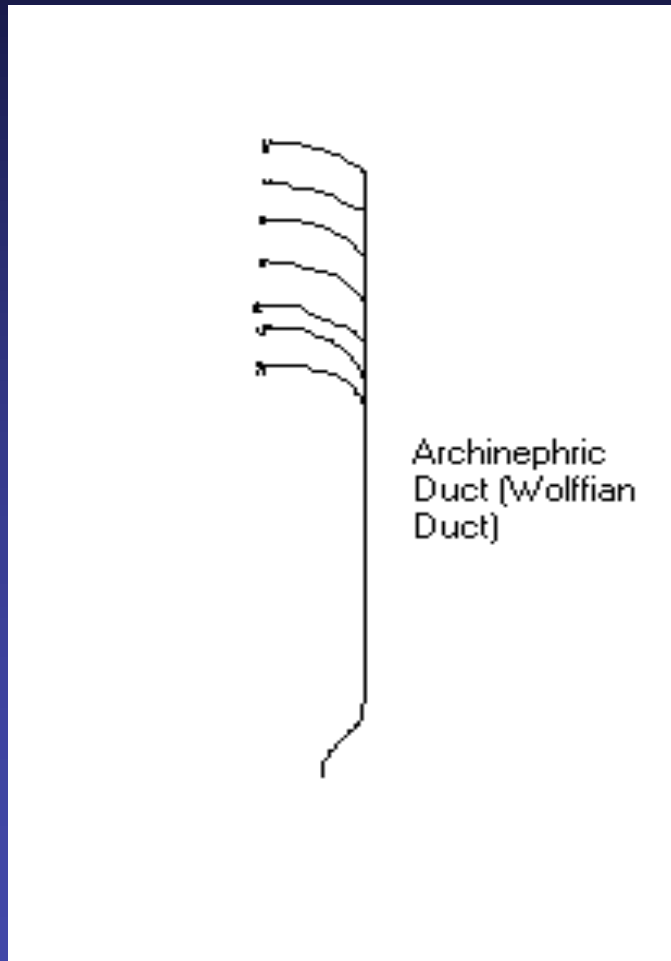


- first description by Johannes Peter Muller in 1830
- origin of the Mullerian duct remains controversial
- lineage-tracing experiments in chicken and mouse embryos
 - show that all Mullerian duct components derive from the coelomic epithelium
 - Mullerian epithelial tube derived from an epithelial anlage at the mesonephros anterior end,
 - segregates from the epithelium and extends caudal of its own accord
 - via a process involving rapid cell proliferation
 - tube is surrounded by mesenchymal cells derived from local delamination of coelomic epithelium
 - no significant influx of cells from the Wolffian duct
 - no support that the tube forms by coelomic epithelium invagination along the mesonephros

Evolution and Embryonic development of the duct system in males

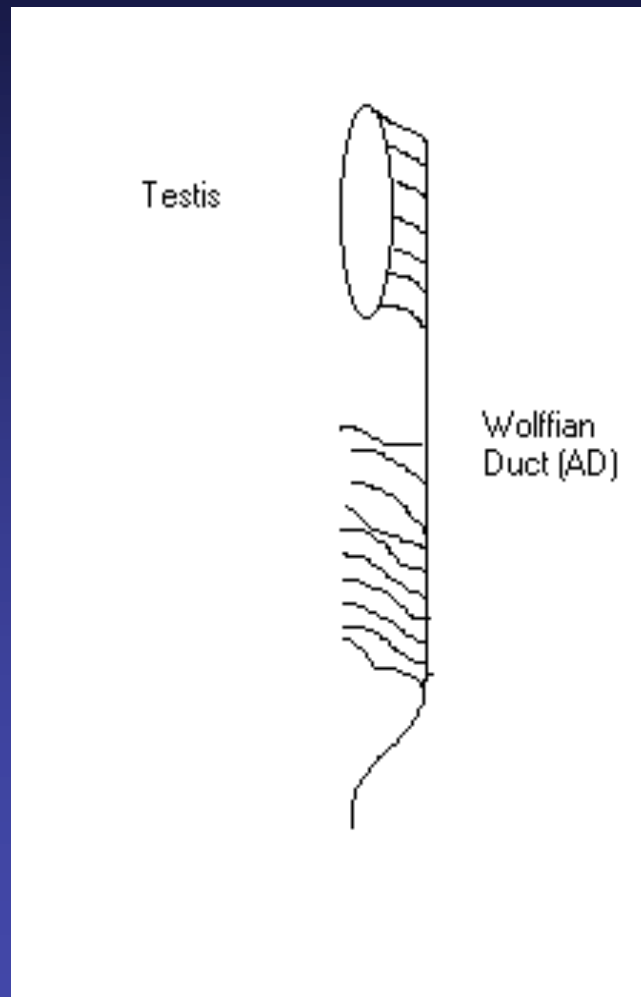
- pronephric kidney
- mesonephric kidney
- metanephric kidney

Pronephric kidney



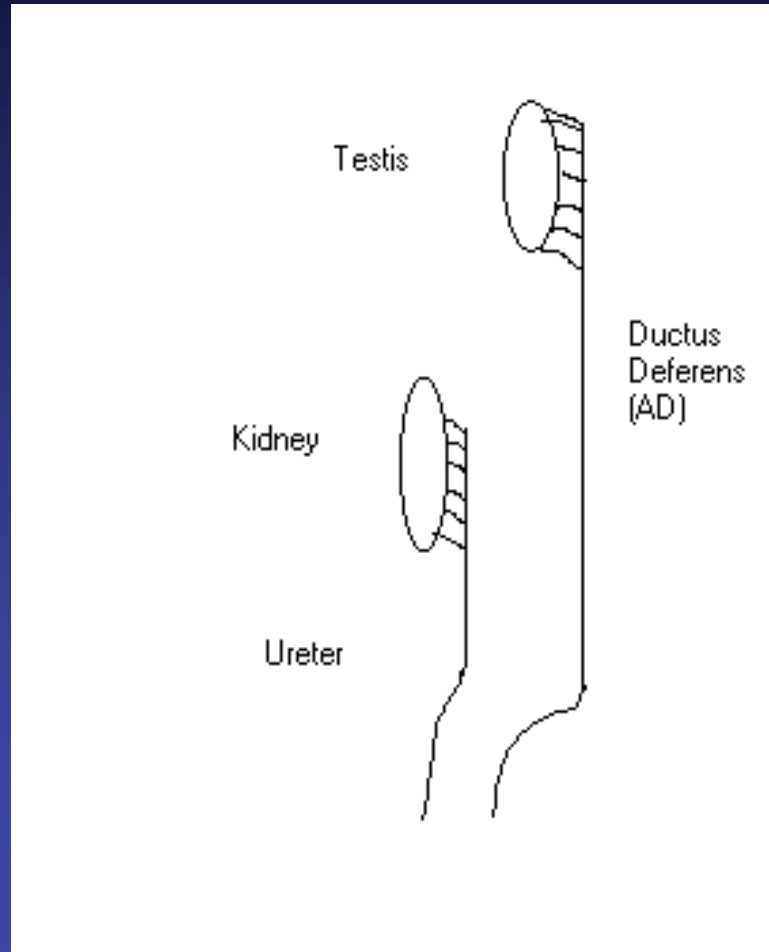
- **1st kidney to form in humans**
 - * It is the **functional kidney** of fish and larval amphibians
- Develops anteriorly then degenerates in amniotes
- Remaining duct called the Wolffian Duct (AD)
 - Sperm transport in amniotes

Mesonephric Kidney



- 2nd kidney
- 30 tubules form in humans
- As tubules form caudally the anterior ones die off
- Female mammals- all tubules die
- Male mammals- tubules become sperm ducts of testis
- Functional Kidney: anamniotes

Metanephric kidney (metanephros)



- Permanent kidney of amniotes
- Serves both as an excretory and osmoregulatory organ
- Ureter transports urine
- Ductus Deferens (AD) transports sperm

Bipotential Ducts

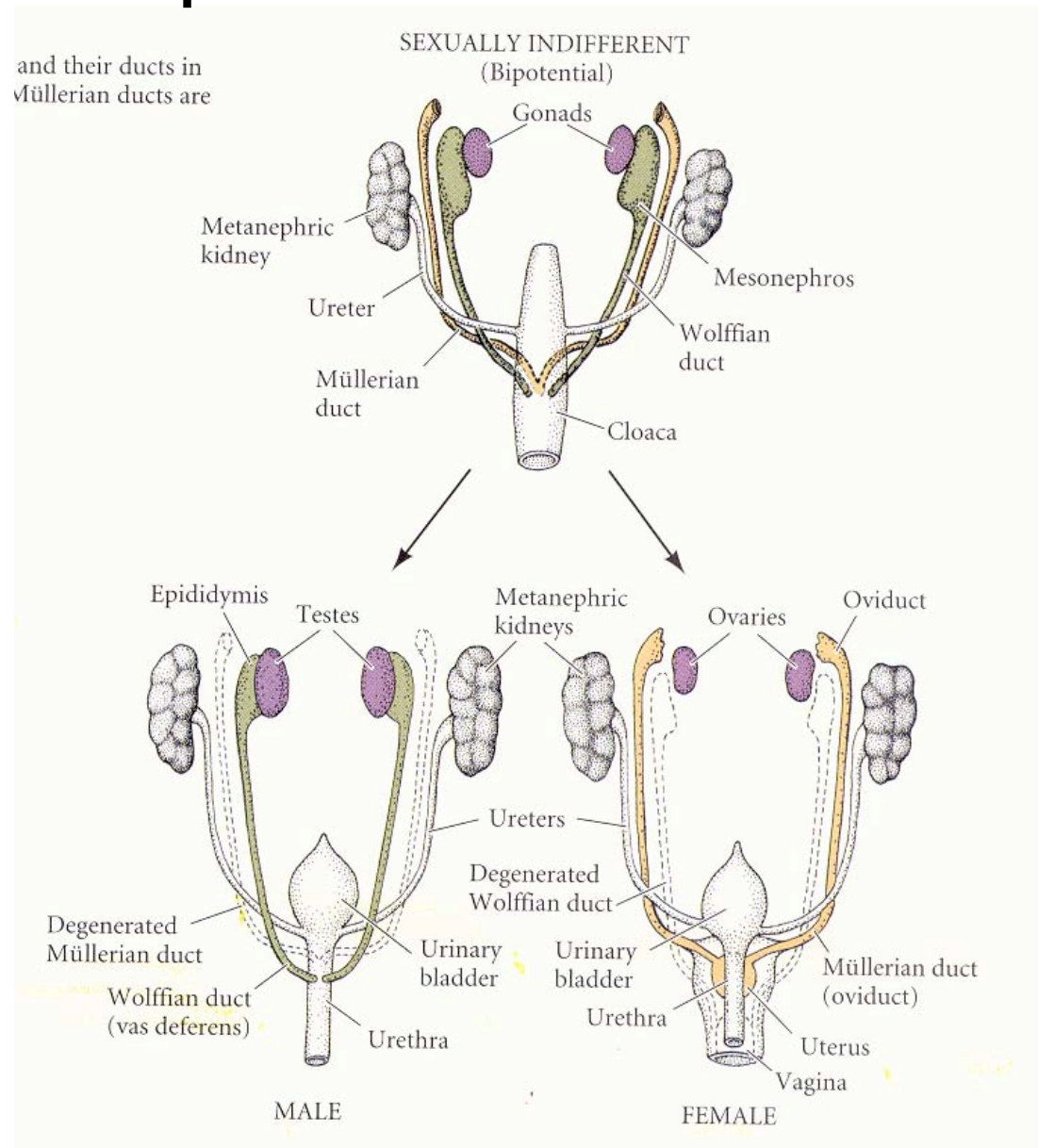


Fig 17.4 Gilbert (2006)
Developmental Biology

Secondary Sex Determination

	Male	Female
Wolffian	+ T	- no T
Mullerian	- MIH	+ no MIH

- Body phenotype
 - e.g., duct system
 - usually determined by hormones
 - a. male = androgens, MIH
 - b. female = no hormones?

Testicular Feminization

Androgen insensitivity syndrome

	Male	Female	TFS
Wolffian	+ T	- no T	? /no
Mullerian	- MIH	+ no MIH	? /no

- XY genetics
- Lack functional androgen receptor
- Testicular formation
- Female external phenotype
- Duct system ?

"Guevodoces"

- "Guevodoces" - "eggs at 12" (Dominican Republic)
 - a. lack functional gene for 5α -reductase 2
 - b. born with blind vaginal sac or poorly fused labia
 - c. at puberty - 12 years - tissue become responsive to testosterone
 - -masculinization of penis, pubic hair - not facial hair
 - -descent of testis into "scrotum"
 - "eggs at 12"- infertile

Some web sites

- <http://www.pbs.org/wgbh/nova/miracle/determined.html#>
- <http://herkules oulu.fi/isbn951426844X/html/i231654.html>