



# SEX DETERMINATION

## (Chromosomal & Environmental)

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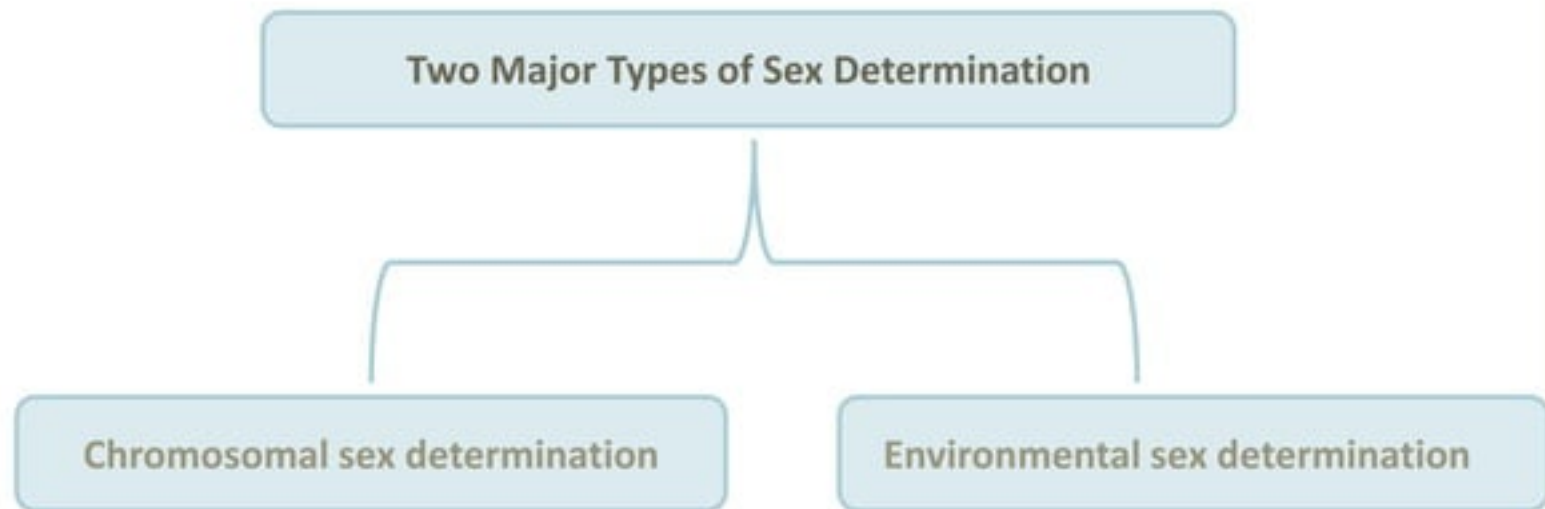
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# Outline

- Sex Determination definition.
- Chromosomal Sex Determination.
  - ✓ Primary sex determination.
  - ✓ Secondary Sex determination.
  - ✓ Genetic mechanism.
- Environmental Sex Determination.
- Conclusion.
- References.

# Sex Determination

- **Sex-determination** mechanisms are responsible for the sexual fate and development of sexual characteristics in an organism.



# Chromosomal sex determination

- In this system, the sex of an individual is determined by a pair of sex chromosomes.
- Chromosomal Sex determination was discovered in the **mealworm** by the American geneticist **Nettie Stevens** in 1903.
- Dr. Stevens observed;  
Sperm carried 19 large chromosomes, and one small chromosome

↓  
**Male offspring**

Sperm carried 20 large chromosomes, and no small ones

↓  
**Female offspring**



Presence of a **different sex chromosome or dosage** plays the vital role in determining the sex of offspring.

### XX,X0 System

XX: Female  
X0: Male



### ZW, ZZ System

ZW: Female  
ZZ: Male  
Sex determined by **Female**



### Sex (X): Autosome ratio System



**Ratio of 1** : Female  
**Ratio of 0.5** : Male  
\*Presence of Y chromosome does not affect the sex of flies

## Chromosomal sex determination

### XX,XY System



XX: Female  
XY: Male  
Sex determined by **Male**

### Haplodiploid System



Diploid (fertilized egg) :  
Female  
Haploid (Unfertilized egg):  
Male  
\*Set of chromosome

# Sex Determination in Human

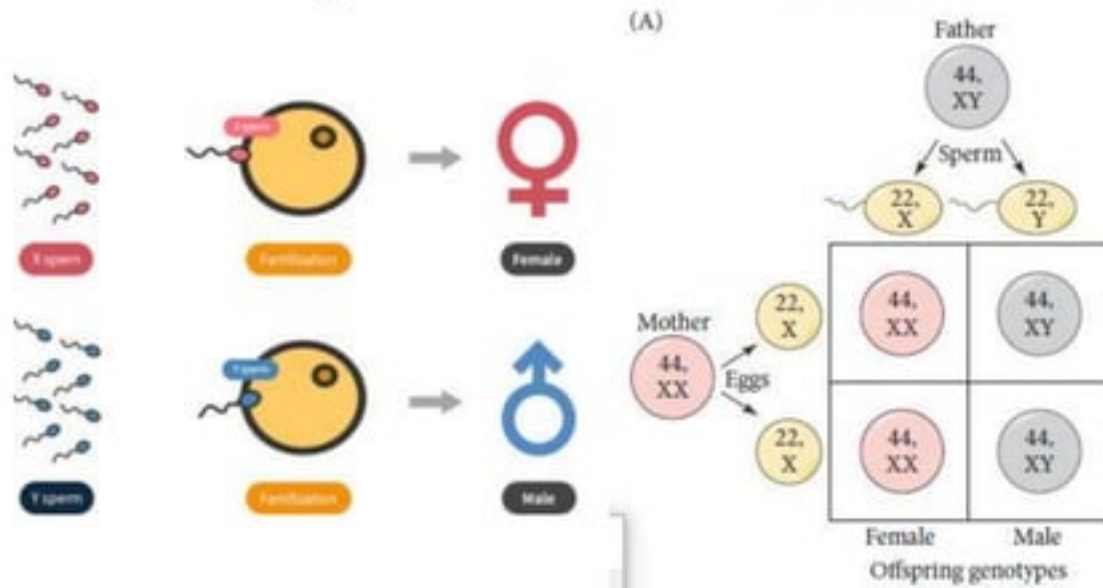
There are 3 levels to sexual development:

1. Chromosomal sex
  - X sperm or Y sperm fertilize with oocyte.
2. Gonadal sex (**primary sex determination**).
  - *is the determination of the gonads—the egg-forming ovaries or sperm-forming testes*
3. Phenotypic sex (**secondary sex determination**).
  - *is the determination of the male or female phenotype by the hormones produced by the gonads.*



# Sex chromosome

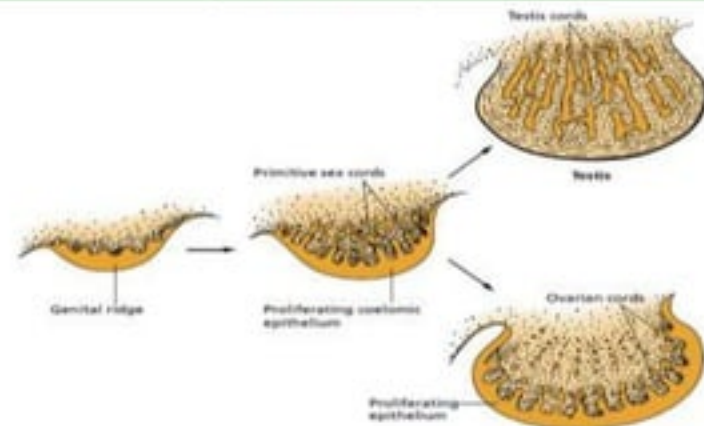
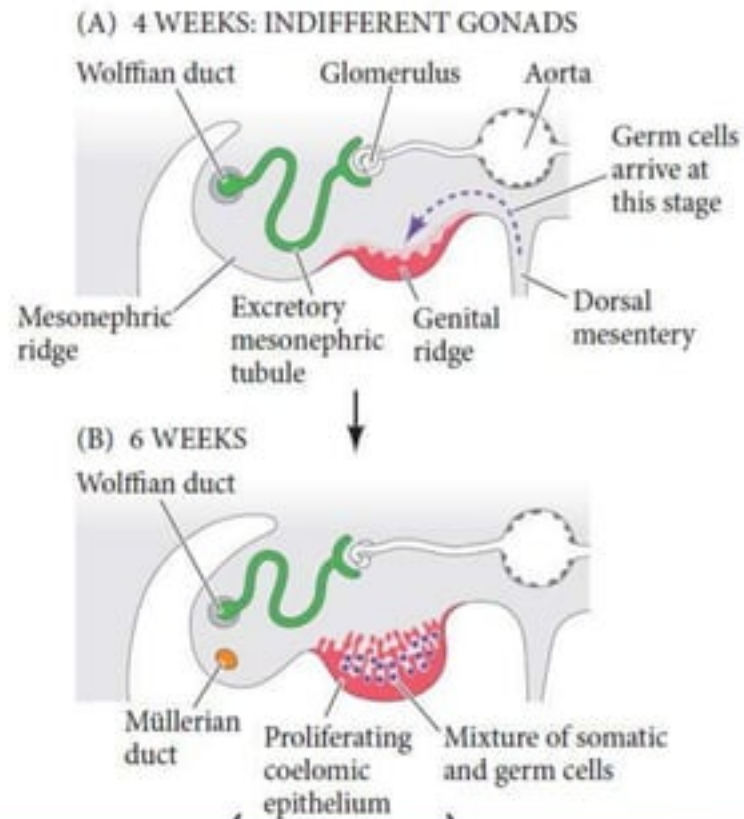
- Sex determination establish of chromosomal sex at the time of gamete fertilization. **How?**



- Females are homomorphic (XX) and males have heteromorphic sex chromosomes (XY).

# The developing gonads

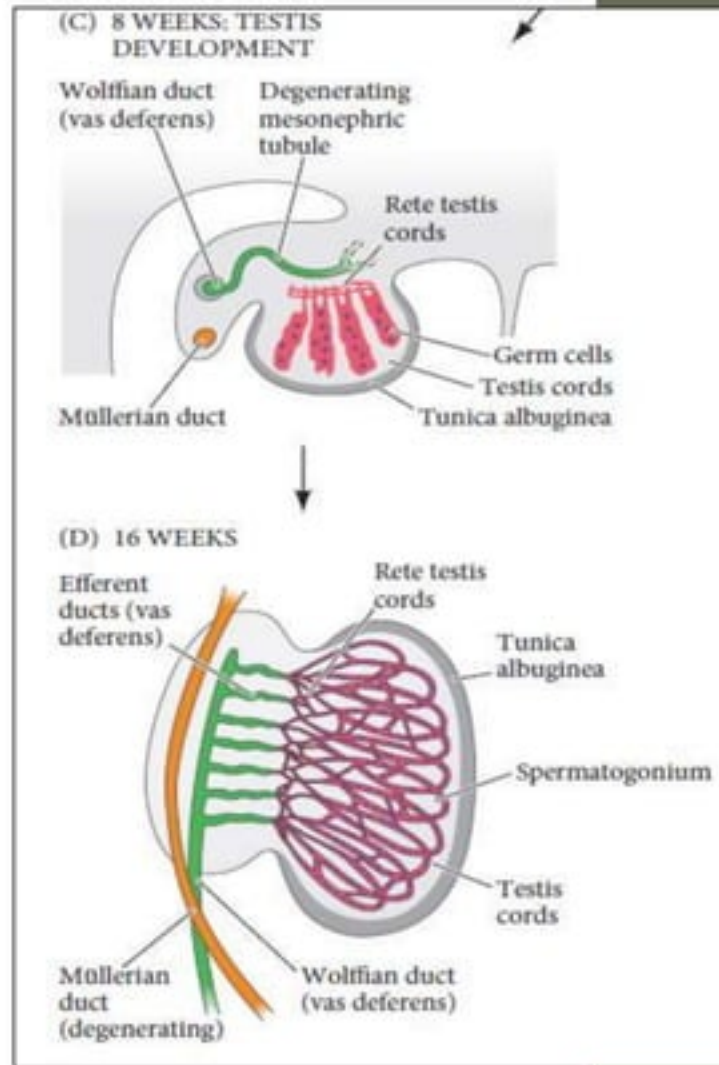
- The **gonads (sex gland)** are both the repositories of the **gametes** and important **endocrine organs**.
- The somatic tissues of the gonads arise from **genital ridges** which are formed from the **intermediate mesoderm**.
- The **genital ridge** exist in a bipotential state, with the competence to develop into either testes or ovaries.
- At week 6, The germ cells migrate into the gonads and surrounded by the mesodermal cells (**Sex cord cell**).
- Cords of cells begin to form from the coelomic epithelium and grow into the underlying mesenchyme.
- Two ducts arise, the **Wolffian duct** in male and the **Müllerian duct** in female.





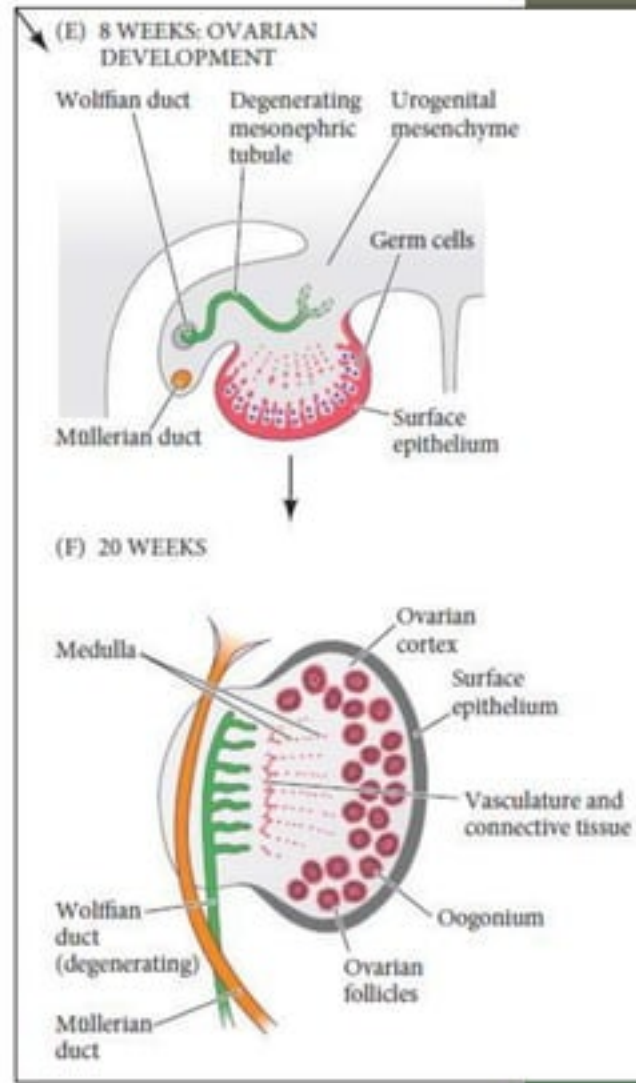
- If fetus is XY, at week 8,16

- Sex cord continue to proliferate into testis cords, which help to develop **Sertoli cells** (epithelium cell).
- Sertoli cells secrete **anti-Müllerian hormone** that block development of the female.
- Sertoli cells and the migrate germ cells organize themselves into **testis cords** and **seminiferous tubules** (producing sperm).
- Other mesoderm cells differentiate into **Leydig cells** (mesenchymal cell).
- Leydig cells secrete testosterone stimulate the **Wolffian duct** differentiates into external genital.



- If the fetus is XX, at week 8,20

- The sex cords **degenerate** and leaving sex cords at the surface (cortex) of the gonad (**cortical cord -epithelial cell**).
- Cortical cord **differentiate** into **granulosa** cells.
- The remaining mesenchyme cells of the developing ovary differentiate into **thecal cells**.
- The thecal and granulosa cells form **follicles** that envelop the germ cells and secrete **steroid** hormones.
- Each follicle contains a **single** germ cell an oogonium.
- **Müllerian duct** remains and absence of testosterone, the Wolffian duct degenerates.



# Hormonal Regulation of the Sexual Phenotype

- It is the development of the female and male phenotypes in response to hormones secreted by the ovaries and testes.
- Both female and male secondary sex determination have two major phases.
- The first phase occurs within the embryo during organogenesis; the second occurs at puberty.

• **Testosterone** → The Wolffian ducts → epididymis and vas deferens.

• **Dihydrotestosterone (DHT)** → The genital tubercle, genital swelling and urogenital sinus → Penis, scrotum and Prostate.

• **Anti-müllerian hormone** degeneration of the Müllerian duct.

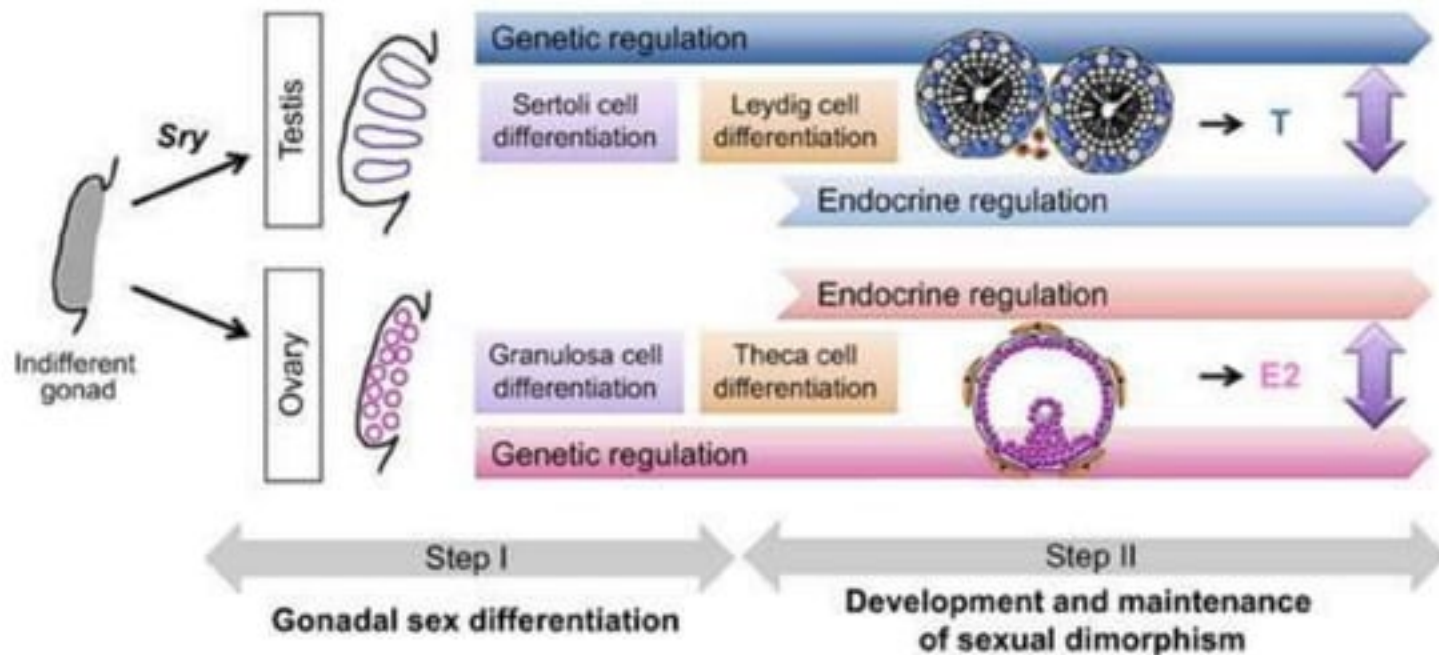
• **Estrogen** → The Müllerian ducts → The uterus, cervix, oviducts, and upper vagina.

• **Absence of AMH and DHT** → The genital tubercle, genital swellings and urogenital sinus → Clitoris, labia majora and Skene's glands.



<b>GONADS</b>		
Gonadal type	Testis	Ovary
Germ cell location	Inside testis cords (in medulla of testis)	Inside follicles of ovarian cortex
<b>DUCTS</b>		
Remaining duct	Wolffian	Müllerian
Duct differentiation	Vas deferens, epididymis, seminal vesicle	Oviduct, uterus, cervix, upper portion of vagina
<b>UROGENITAL SINUS</b>	Prostate	Skene's glands
<b>LABIOSCROTAL FOLDS</b>	Scrotum	Labia majora
<b>GENITAL TUBERCLE</b>	Penis	Clitoris

**FIGURE 6.1** Development of gonads and their ducts in mammals. Originally, a bipotential (indifferent) gonad develops, with undifferentiated Müllerian ducts (female) and Wolffian ducts (male) ducts both present. If XY, the gonads become testes and the Wolffian duct persists. If XX, the gonads become ovaries and the Müllerian duct persists. Hormones from the gonads will cause the external genitalia to develop either in the male direction (penis, scrotum) or the female direction (clitoris, labia majora).



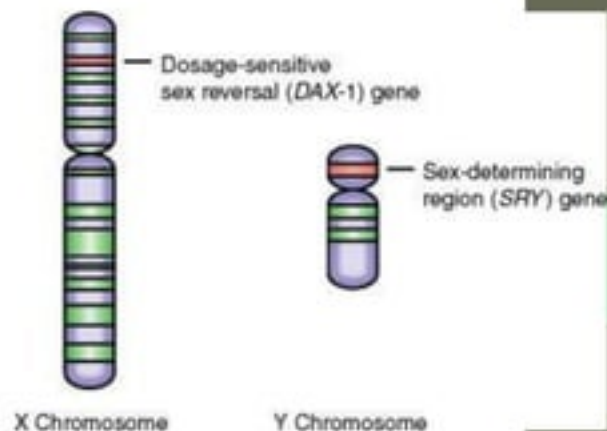
# Genetic mechanisms of sex determination

- The **bipotential gonad** differentiated through genes for transcription factors **Wt1**, **Lhx9**, **GATA4**, and **SF1** are expressed in the normal development of either male or female gonads.

- Then the decision is made that depend on:

**Y chromosome** (Testis-determining factor (TDF), also known as sex-determining region Y (SRY) .

**Two X chromosomes** have DAX1 gene (anti-testis gene) and play role in regulating hormone production





- Molecular mechanisms of sex determination by focusing on the known critical sex determining genes and their related signaling pathways( She and Yang, 2014).

## XX- Female

- Sex chromosome

DAX1 Gene (on both X-chromosome)

- Autosomes

WNT-4 Gene

RSPO-1 Gene

## XY- Male

- Sex chromosome

SRY Gene: on Y chromosome.

DAX1 Gene: X chromosome

- Autosomes

SF1 Gene

FGF9 Gene

SOX9 Gene

WT1 Gene

### Molecular mechanisms involved in mammalian primary sex determination

In Journal of Molecular Endocrinology

Authors: Zhen-Yu She and Wan-Xi Yang

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- If Y chromosome **ABSENT**

**Rspo1** binds to its cell membrane receptor and stimulates the the Wnt pathway (Wnt4), then producing the transcriptional regulator  $\beta$ -catenin.

- **$\beta$ -catenin helps with:**

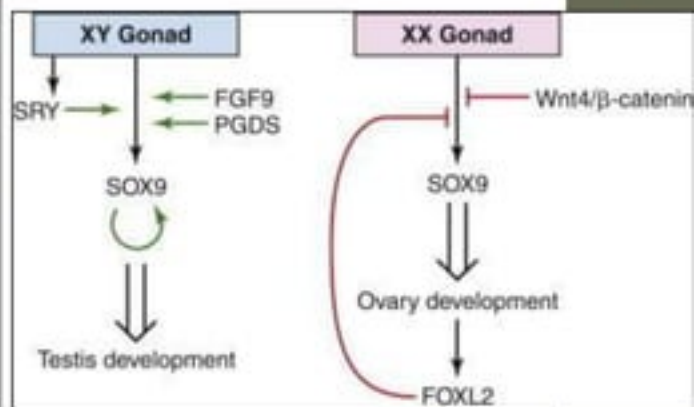
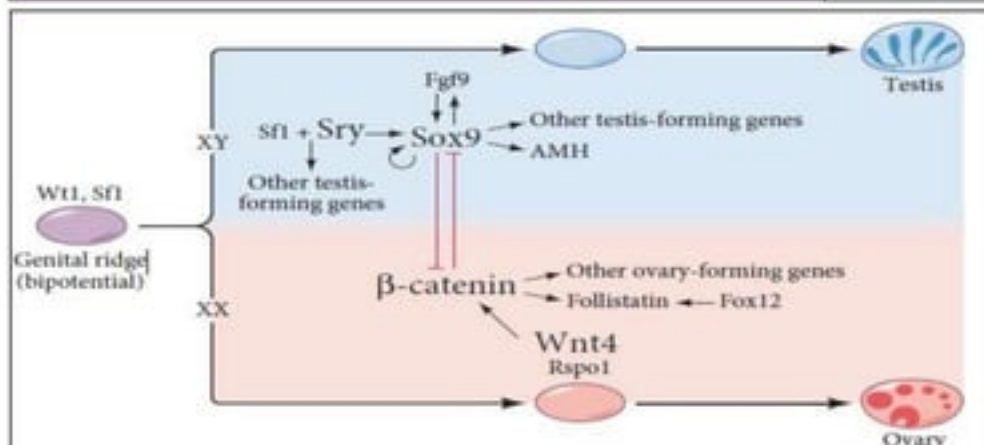
- 1) Activate the genes for Rspo1 and Wnt4, creating a positive feedback.
- 2) Initiate the ovarian pathway of development.
- 3) Prevent the production of Sox9.
- 4) Active other genes in the ovary and produce the granulosa cells.

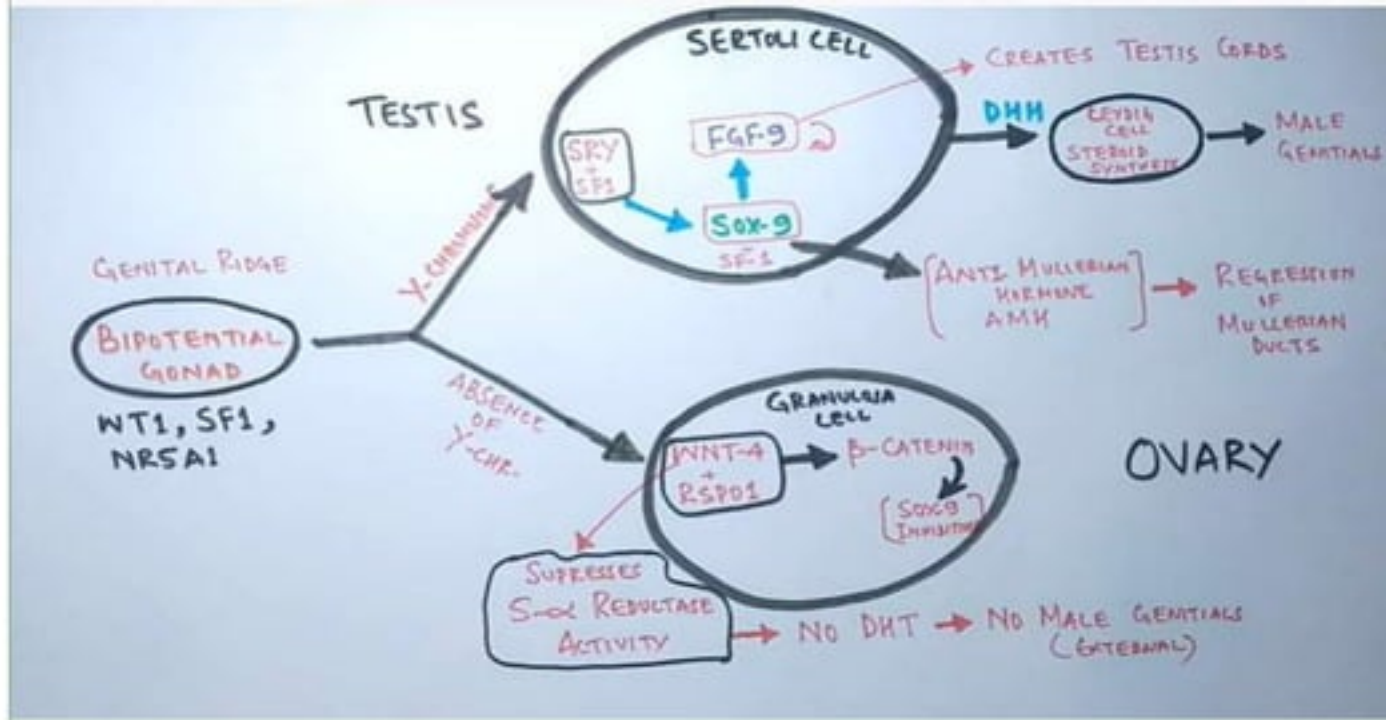
- If a Y chromosome **PRESENT**

**Sry** protein binds to the enhancer Sox9 gene and elevates expression of this key gene in the testis determining pathway.

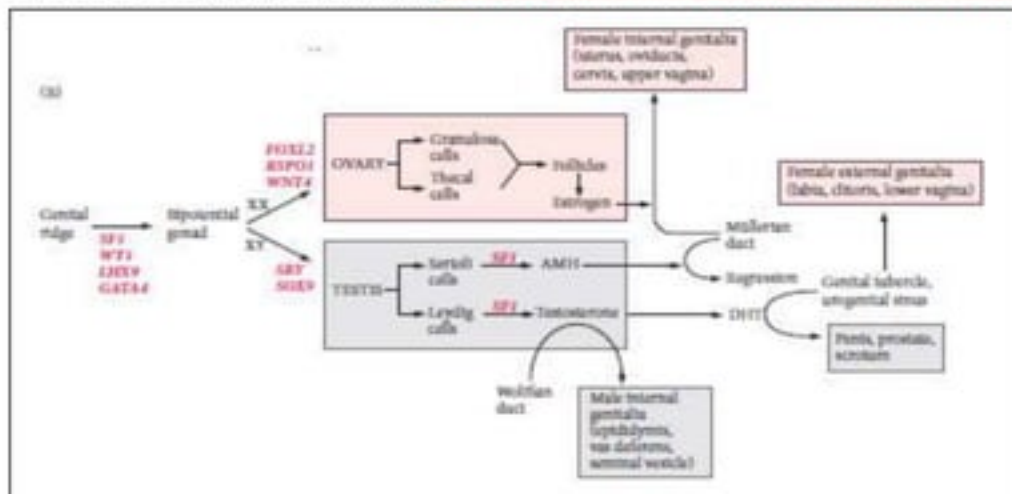
- **Sox9 helps with :**

- 1) Act to block the ovary-forming pathway, by blocking  $\beta$ -catenin.
- 2) Sox9 activates Fgf9 synthesis, which stimulates testis development .
- 3) Activate other genes that help generate Sertoli cells.
- 4) Binds to the promoter site on the gene for anti-Müllerian hormone (AMH).





Sex Differentiation | Molecular Mechanism <https://www.youtube.com/watch?v=Ob8YRELPh3k>





# Sex determination abnormalities

- Abnormal of sex chromosome number or gonadal development lead to develop many disorders of sexual development (DSD) (Witchel, 2018).
- ✓ **Sex reversal:** A genetic decontrol of genes such as *SRY*, *SOX9*, *DAX-1*, *WNT4*, *WT1*, and *SF-1* can result in disorders of sex development (DSD).
- ✓ **Turner Syndrome:** (45,X)
- ✓ **Klinefelter Syndrome:** (47,XXY)

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## DISORDERS OF SEX DEVELOPMENT

[Selma Feldman Witchel](#). MD

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# Environmental Sex Determination

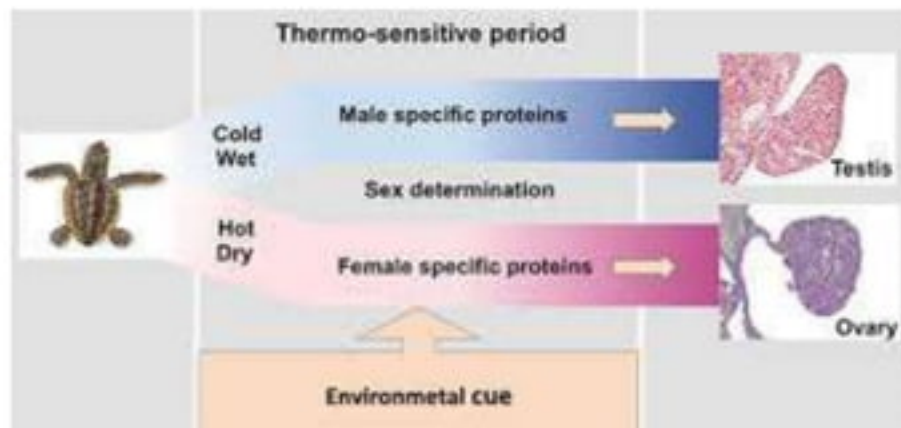
In many organisms, sex is determined by environmental factors such as

- Temperature.
- Location.



# Temperature-induced change

- In Reptiles, the temperature of the eggs during a certain period of development is the deciding factor in determining sex, and small changes in temperature can cause dramatic changes in the sex ratio.
- Eggs incubated at low temperatures (22 -27°C) produce a **male**, whereas eggs incubated at higher temperatures (30°C and above) produce **female**.



# Location dependent

- *Bonellia viridis*, **the green spoon worm**, generates free-swimming larvae.
- Those larvae that reach **sea** bottom develop into **females**.
- Those larvae that land on **a female's body** develop into parasitic **males** who live in the female's reproductive tract.



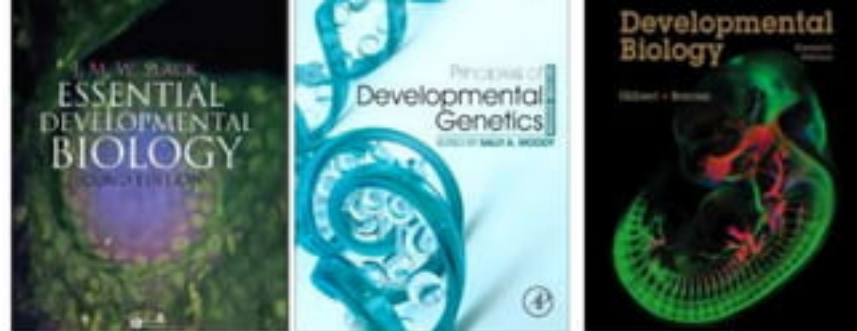
# Do environmental factors affect human sex determination?

- The environment plays critical roles during normal development such as temperature diet and stress .
- The expression of sex-determining genes (*Sox9* and *Sry* in males;  $\beta$ -*catenin* in females) are seen to correlate with male- or female-producing temperatures.
- Genetic studies on the sensitivity of temperature-induced sex determination have pointed to CIRBP (cold-induced RNA-binding protein) as the agent responding to temperature differences).
- Another temperature-sensitive protein that may regulate sex determination is TRPV4, a  $Ca^{2+}$  channel whose activity correlates with activating testes forming genes .

# Conclusion

- A sex-determination system is a biological system that determines the development of sexual characteristics in an organism.
- Two major types of sex determination, chromosomal and environmental.
- Primary sex determination (the determination of gonadal sex) is a function of the sex chromosomes.
- XY and XX mammals both have a bipotential gonad and they are similar until 6 weeks of pregnancy .
- In XY, Sertoli cells, Leydig cells and testosterone help to differentiate testis.
- In XX, granulosa cells, the thecal cells and estrogen help to develop ovary.
- The *SRY*, *SOX9*, *Wnt4* and *Rspo1* genes play a critical roles in male and female differentiation.
- Secondary sex determination involves the factors produced by the developing gonads.
- Environmental sex determination is the establishment of **sex** by a non-genetic cue, such as temperature and localization .

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