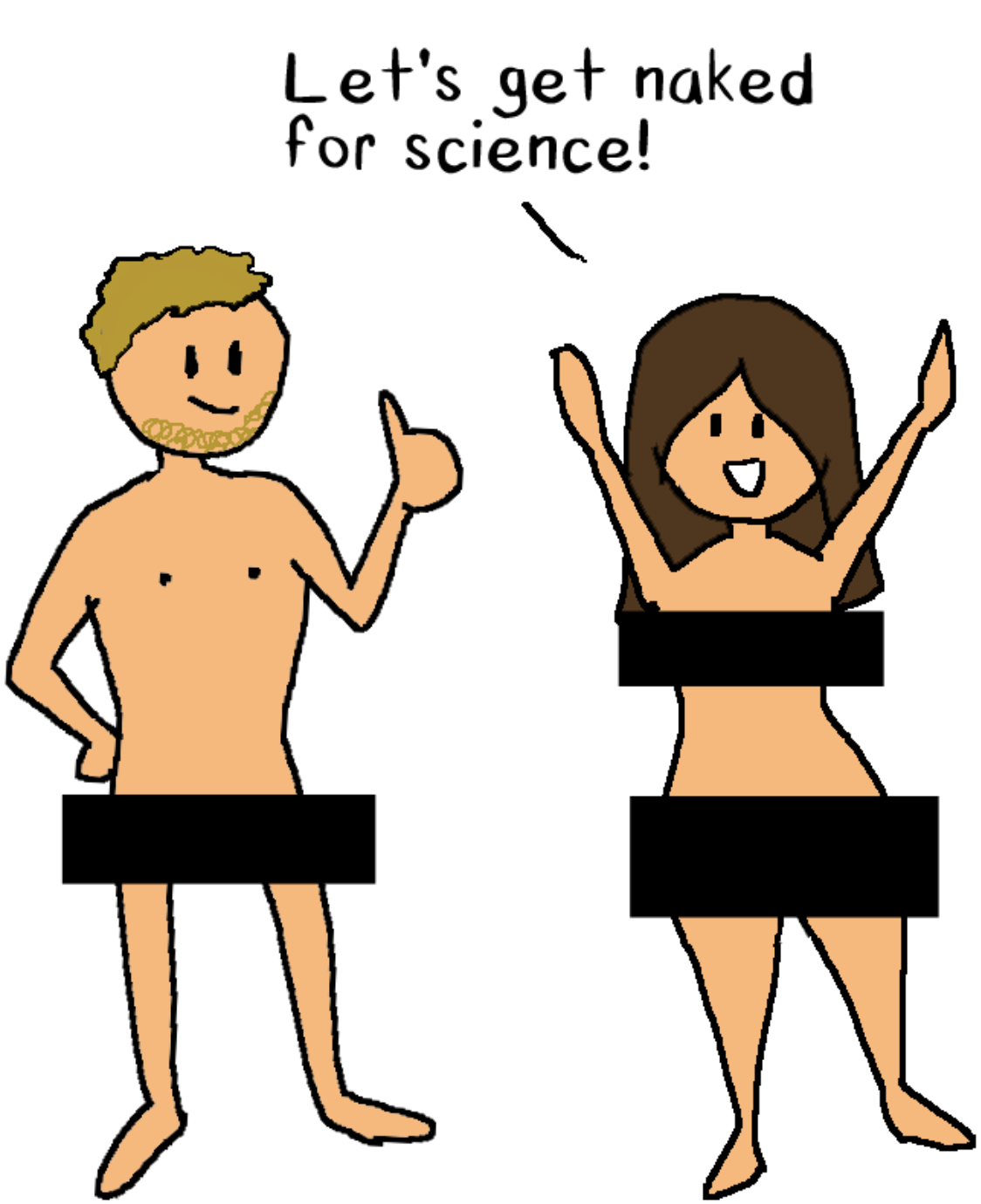
Disorders of gonadal and sexual development

gonadal embryogenesis, cytogenetics/molecular abnormalities, and clinical aspects

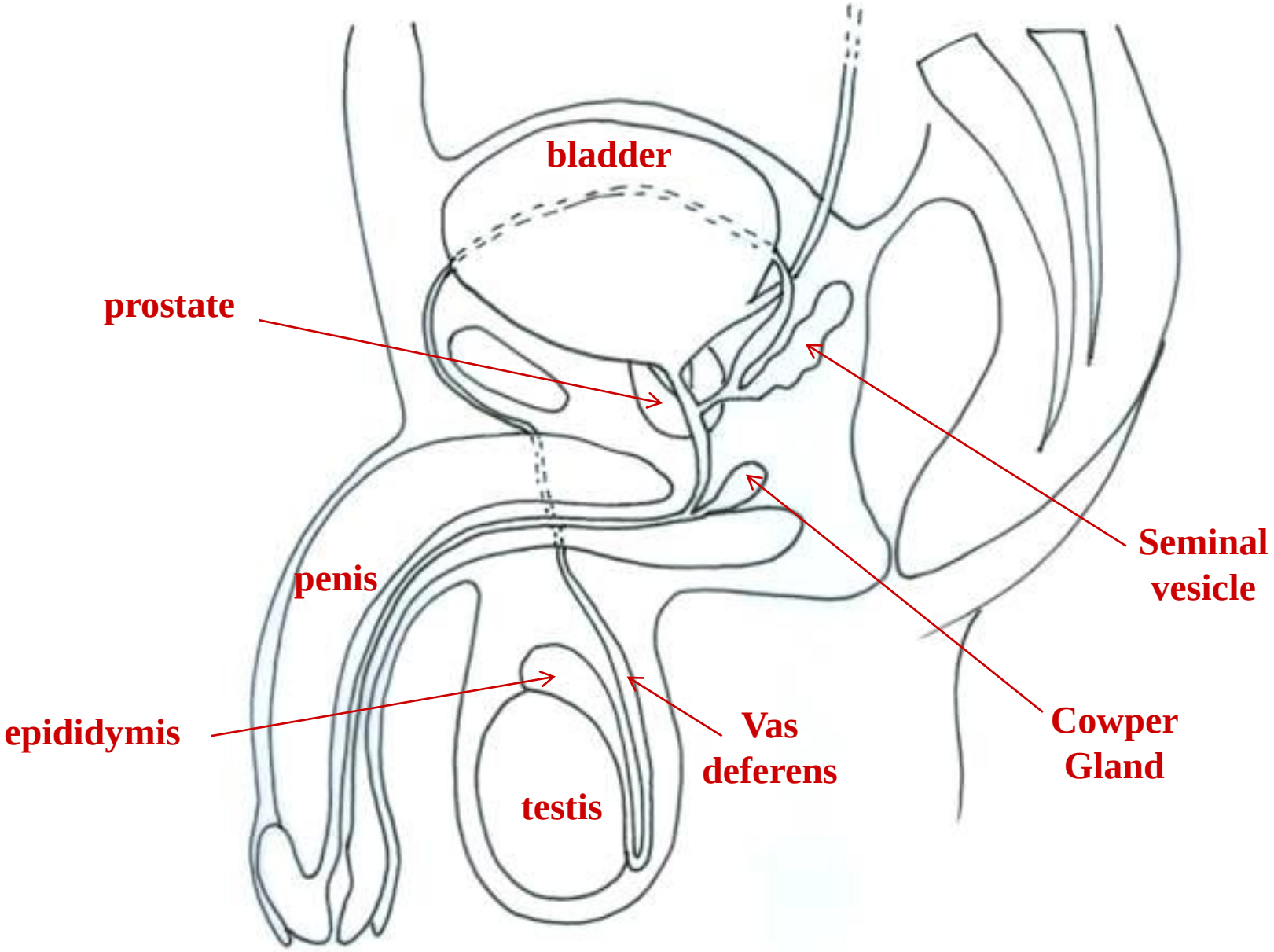
Pr I.Maystadt

19/01/2024

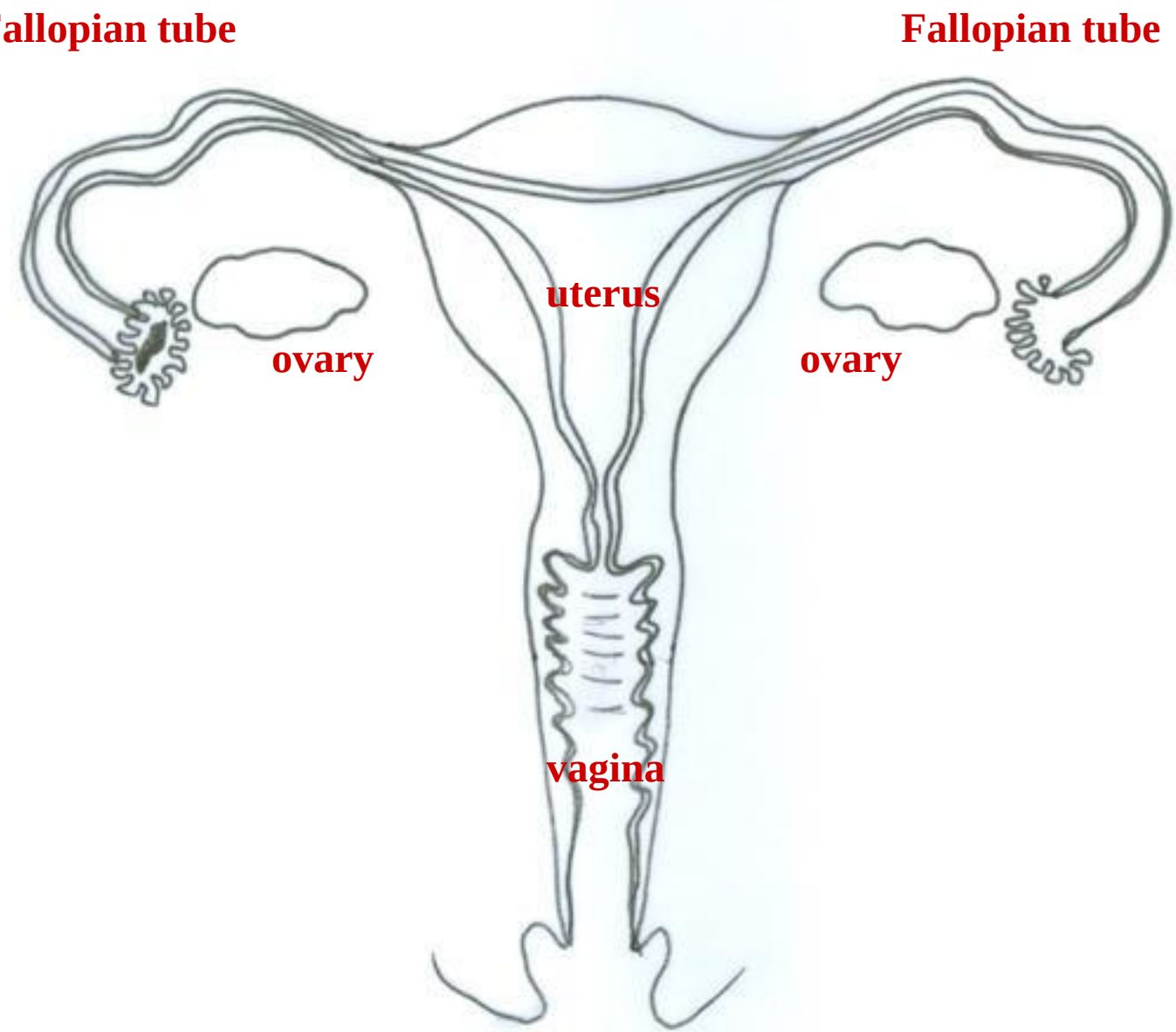
IPG


Let's get naked
for science!

Male Genitalia



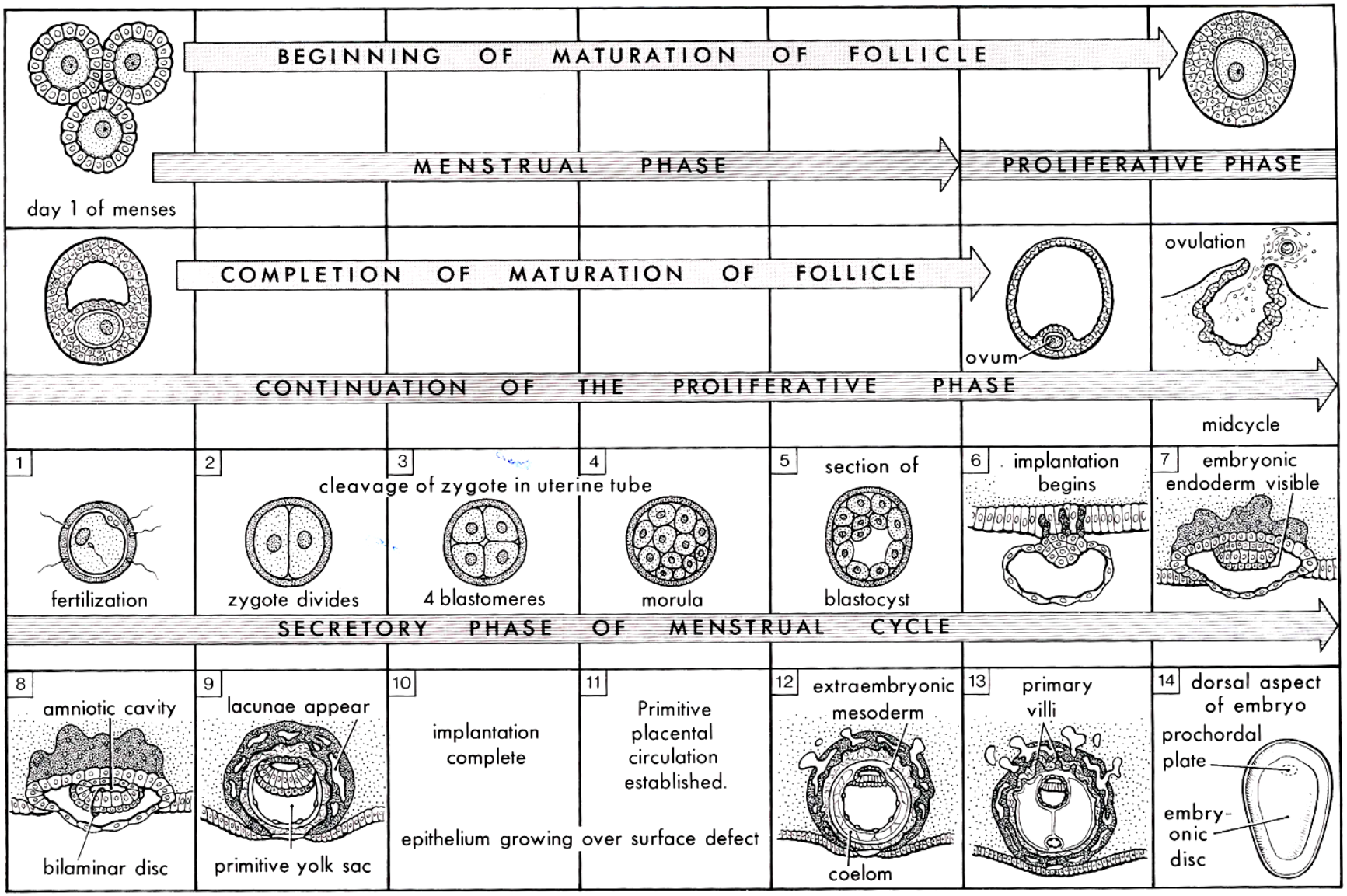
Female Genitalia



GONADAL AND GENITAL EMBRYOGENESIS

TIMETABLE OF HUMAN PRENATAL DEVELOPMENT

1 to 6 weeks

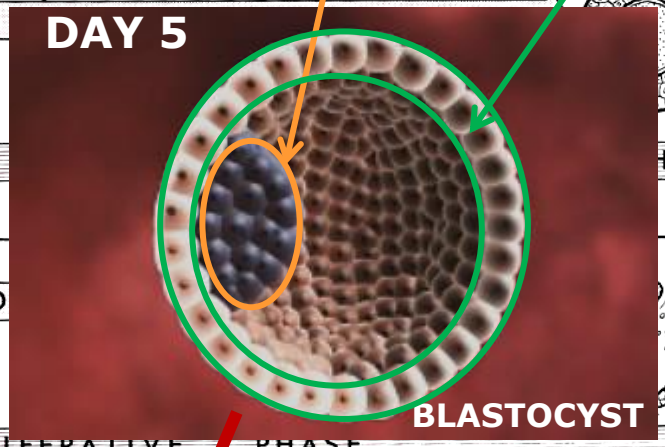


INNER CELL MASS (> embryo)

TROPHOBLAST (> placenta)

TIMETABLE OF HUMAN PRENATAL DEVELOPMENT

1 to 6 weeks



day 1 of menses

midcycle

PROLIFERATIVE PHASE

AGE (weeks)

1

1 fertilization

2 zygote divides

3 4 blastomeres

4 morula

5 blastocyst

6 implantation begins

7 embryonic endoderm visible

SECRETORY PHASE OF MENSTRUAL CYCLE

2

8 amniotic cavity; bilaminar disc

9 lacunae appear; primitive yolk sac

10 implantation complete; epithelium growing over surface defect

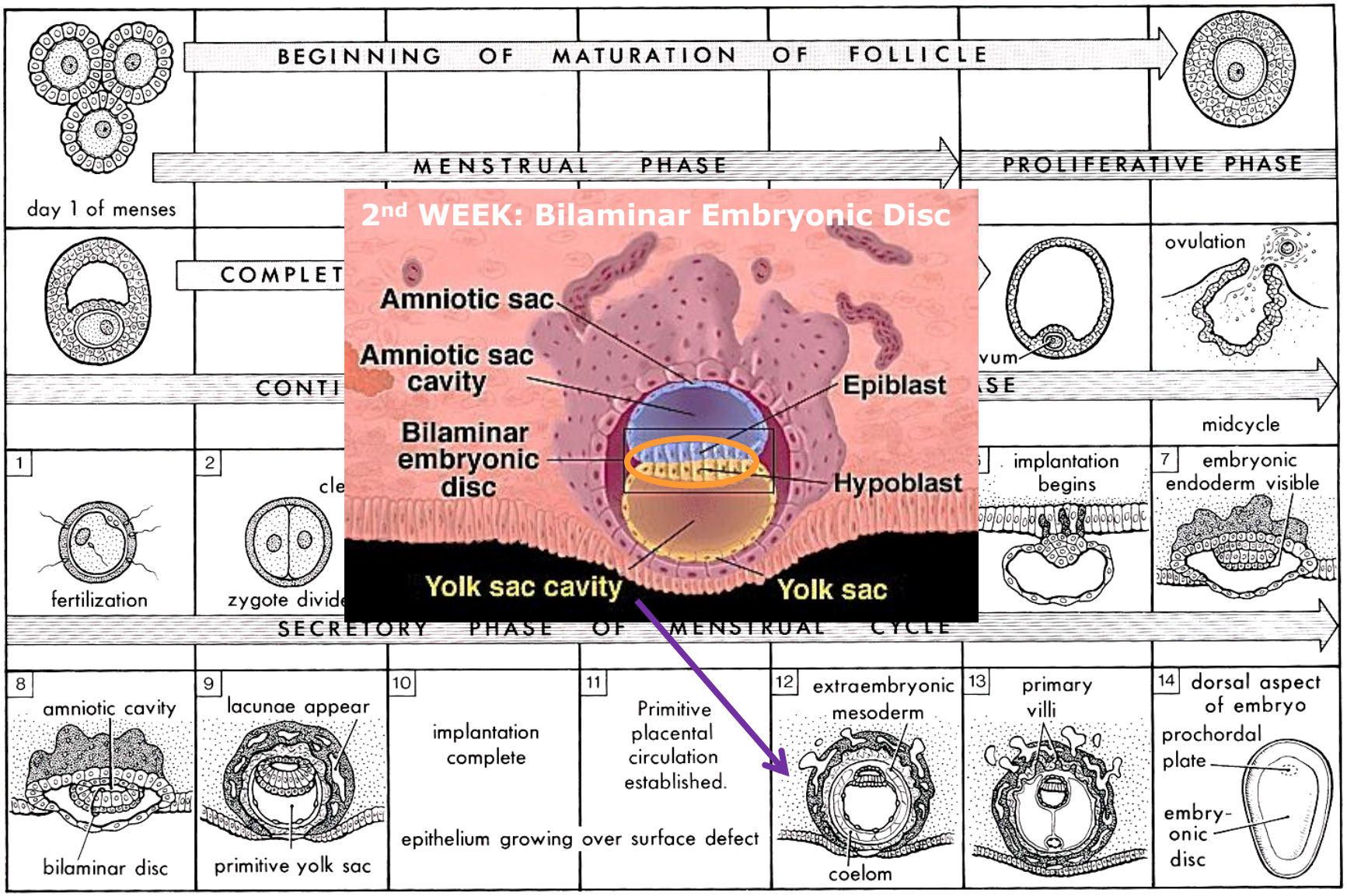
11 Primitive placental circulation established.

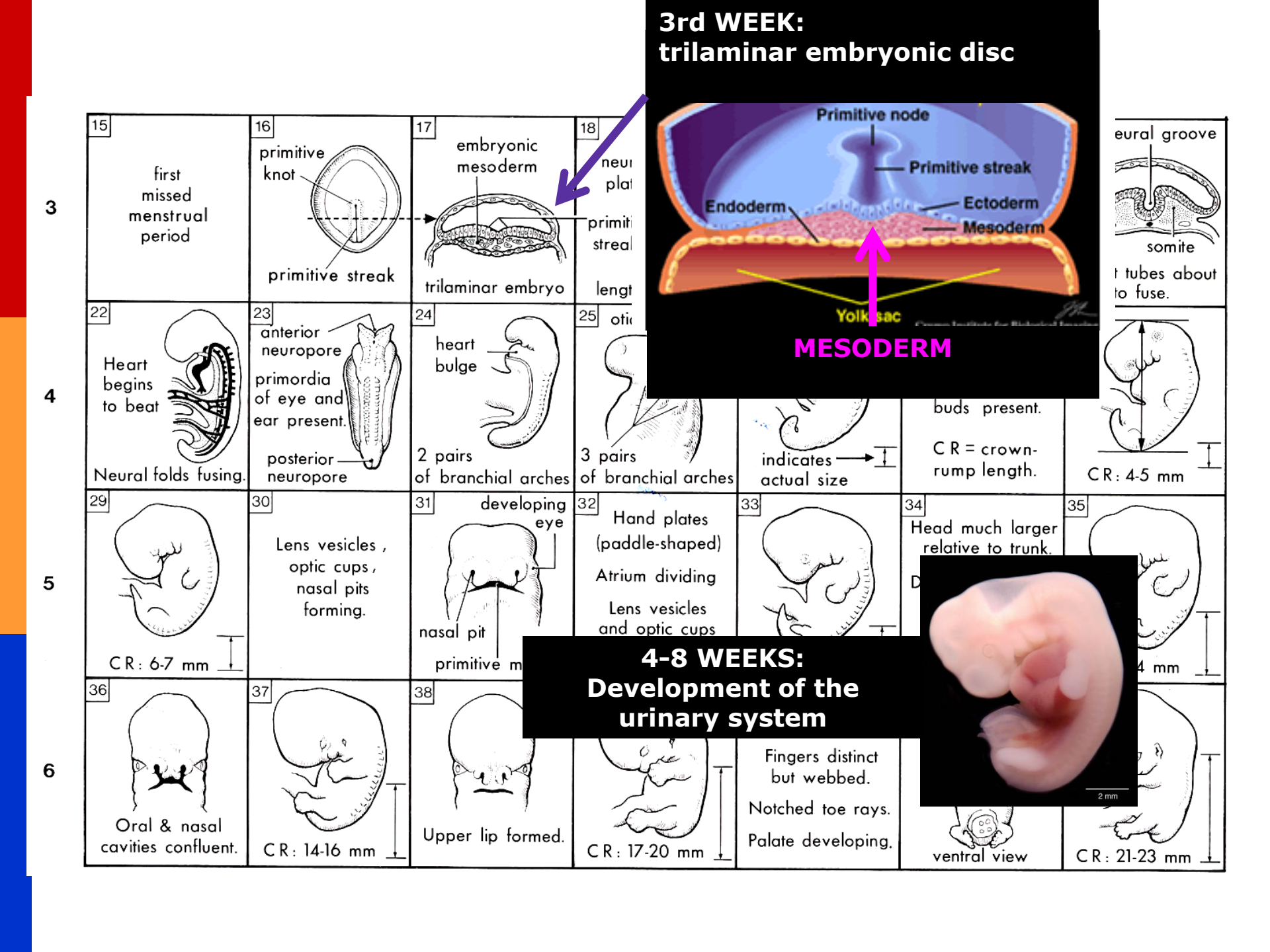
12 extraembryonic mesoderm; coelom

13 primary villi

14 dorsal aspect of embryo; prochordal plate; embry-onic disc

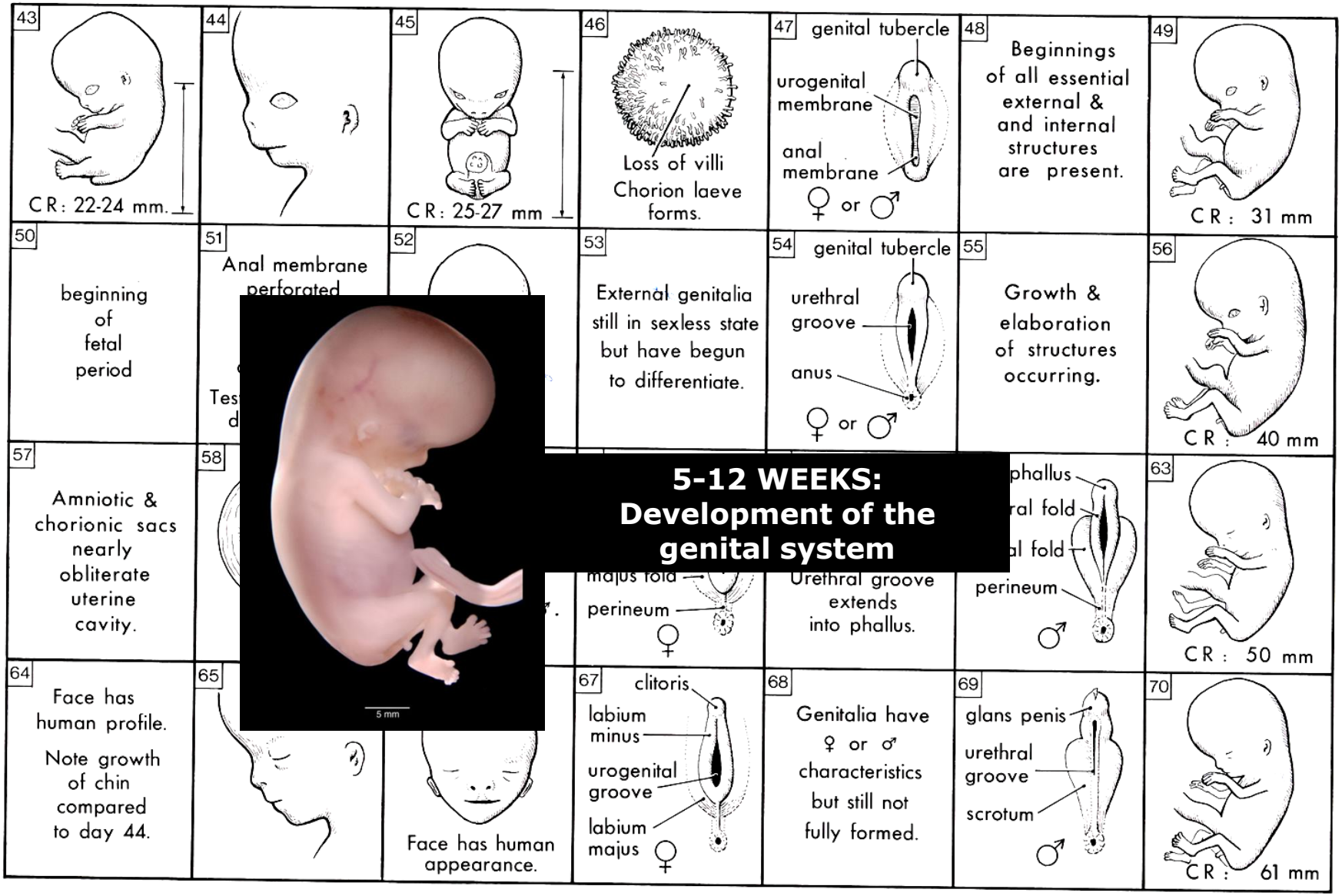
TIMETABLE OF HUMAN PRENATAL DEVELOPMENT
1 to 6 weeks



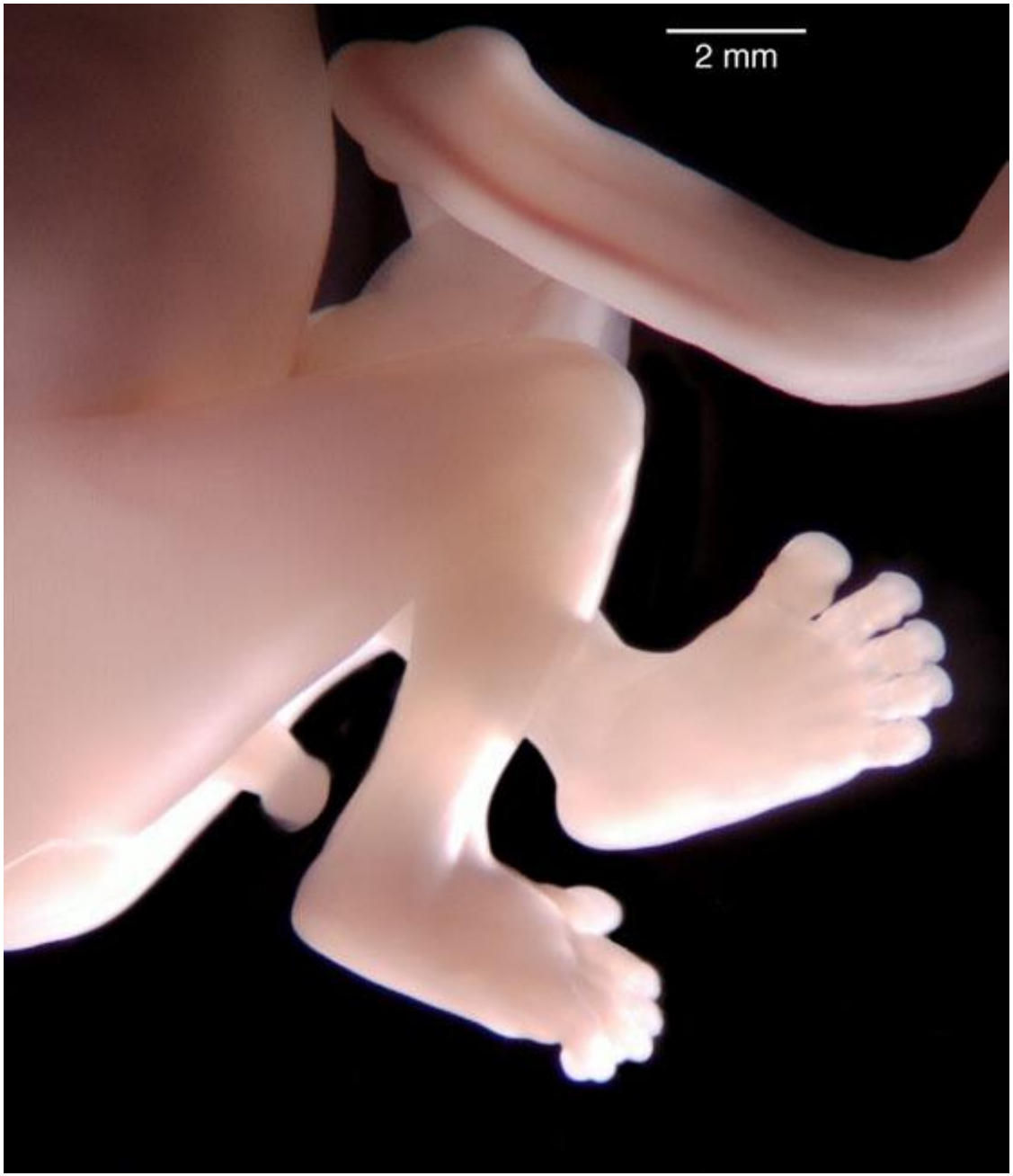

3rd WEEK:
trilaminar embryonic disc
Primitive node
Primitive streak
Endoderm
Ectoderm
Mesoderm
Yolk sac
MESODERM
3
4
5
6
15
first missed menstrual period
16
primitive knot
primitive streak
17
embryonic mesoderm
trilaminar embryo
18
primiti streal
lengt
eural groove
somite
tubes about to fuse.
22
Heart begins to beat
Neural folds fusing.
23
anterior neuropore
primordia of eye and ear present.
posterior neuropore
24
heart bulge
2 pairs of branchial arches
25
3 pairs of branchial arches
indicates actual size
buds present.
C R = crown-rump length.
C R : 4-5 mm
29
C R : 6-7 mm
30
Lens vesicles , optic cups , nasal pits forming.
31
developing eye
nasal pit
primitive m
32
Hand plates (paddle-shaped)
Atrium dividing
Lens vesicles and optic cups
33
34
Head much larger relative to trunk.
35
4 mm
4-8 WEEKS:
Development of the urinary system
2 mm
36
Oral & nasal cavities confluent.
37
C R : 14-16 mm
38
Upper lip formed.
C R : 17-20 mm
Fingers distinct but webbed.
Notched toe rays.
Palate developing.
ventral view
C R : 21-23 mm

TIMETABLE OF HUMAN PRENATAL DEVELOPMENT

7 to 38 weeks



5-12 WEEKS: Development of the genital system

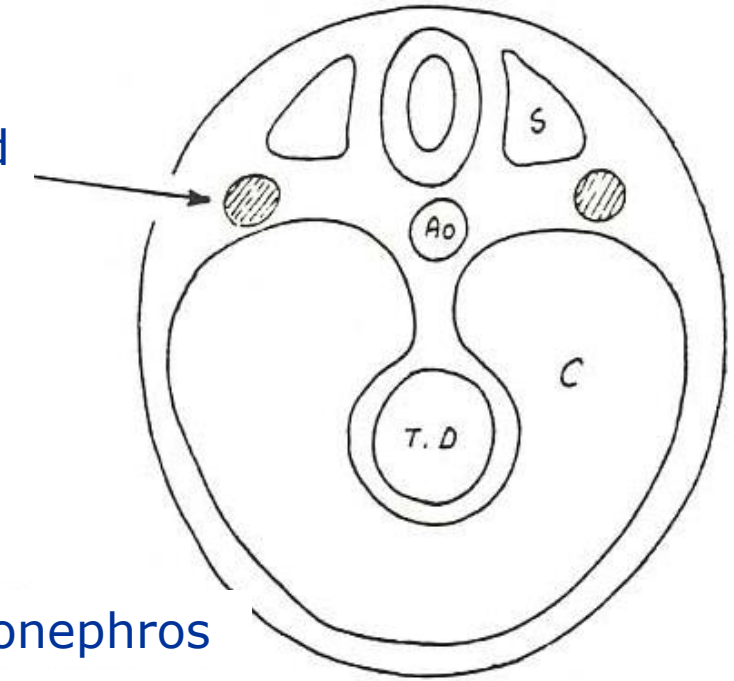


End of the 8th week

Mesoderm differentiation

Mesoderm differentiation

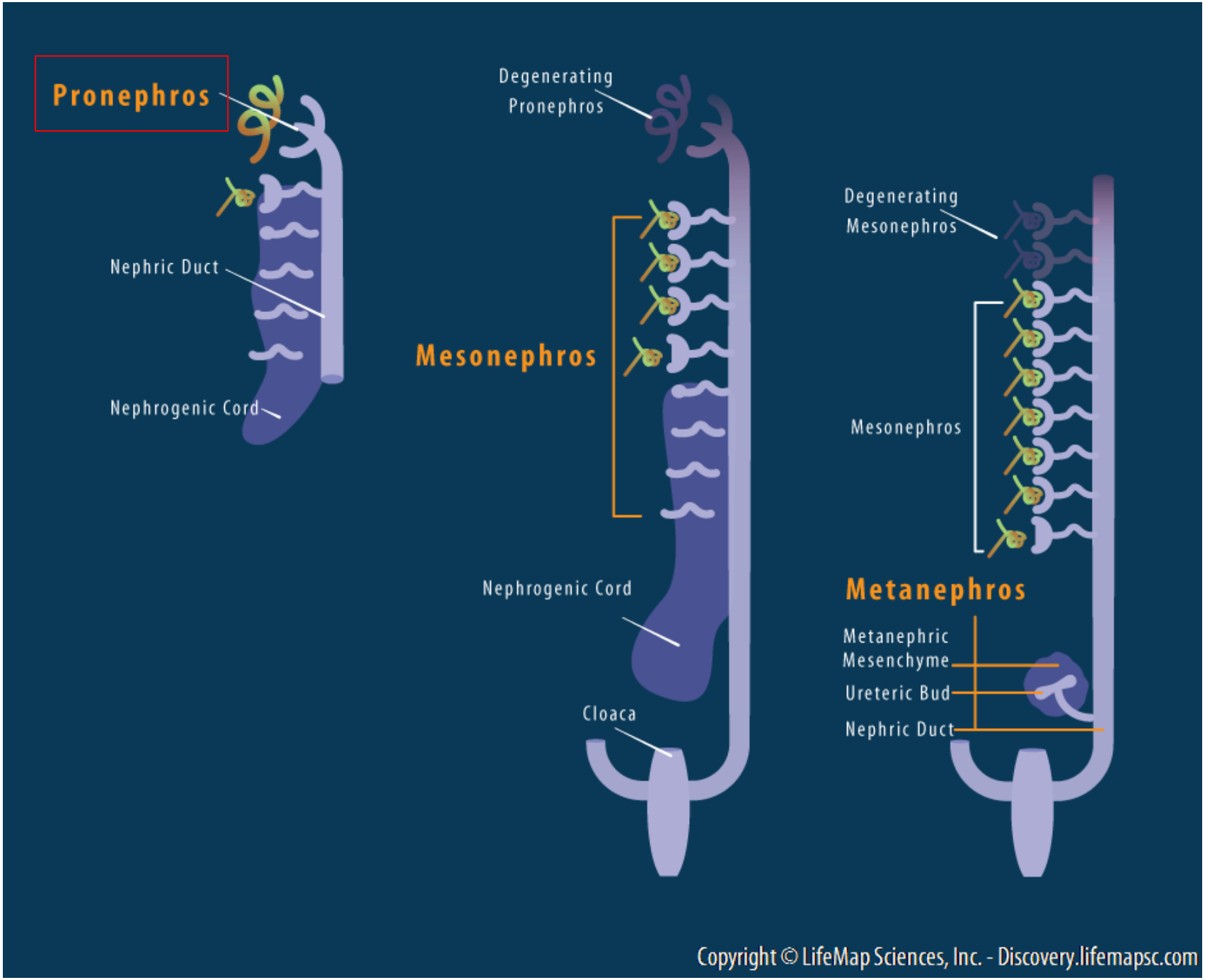
Nephrogenic cord



Pronephros

Mesonephros

Metanephros


Pronephros
Nephric Duct
Nephrogenic Cord
Degenerating
Pronephros
Mesonephros
Nephrogenic Cord
Cloaca
Degenerating
Mesonephros
Mesonephros
Metanephros
Metanephric
Mesenchyme
Ureteric Bud
Nephric Duct
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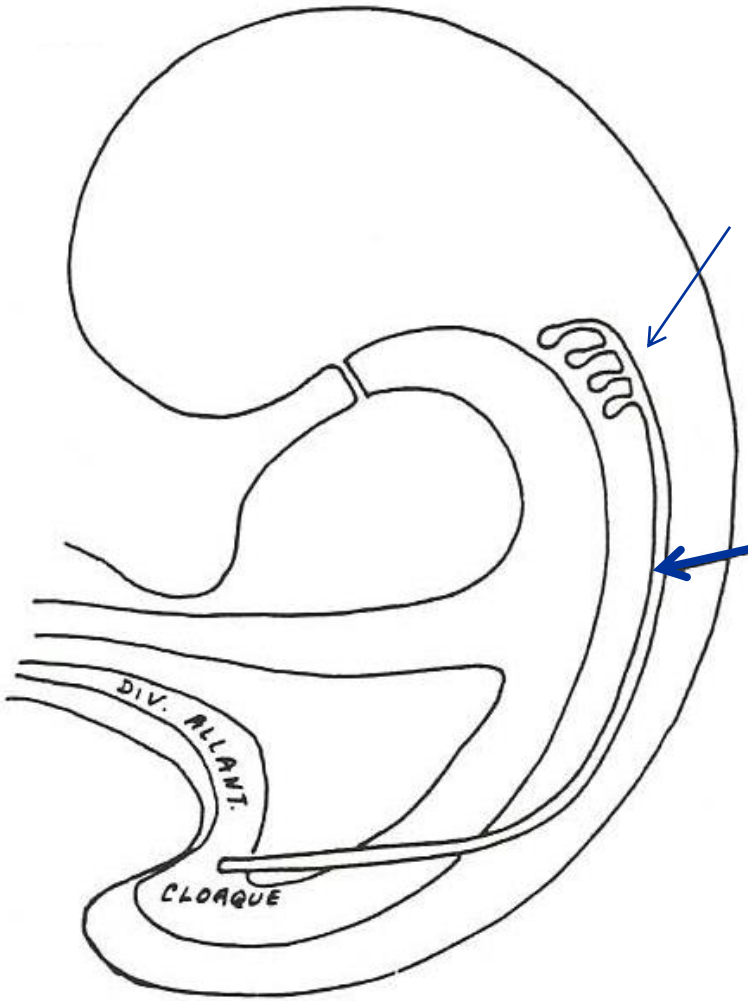
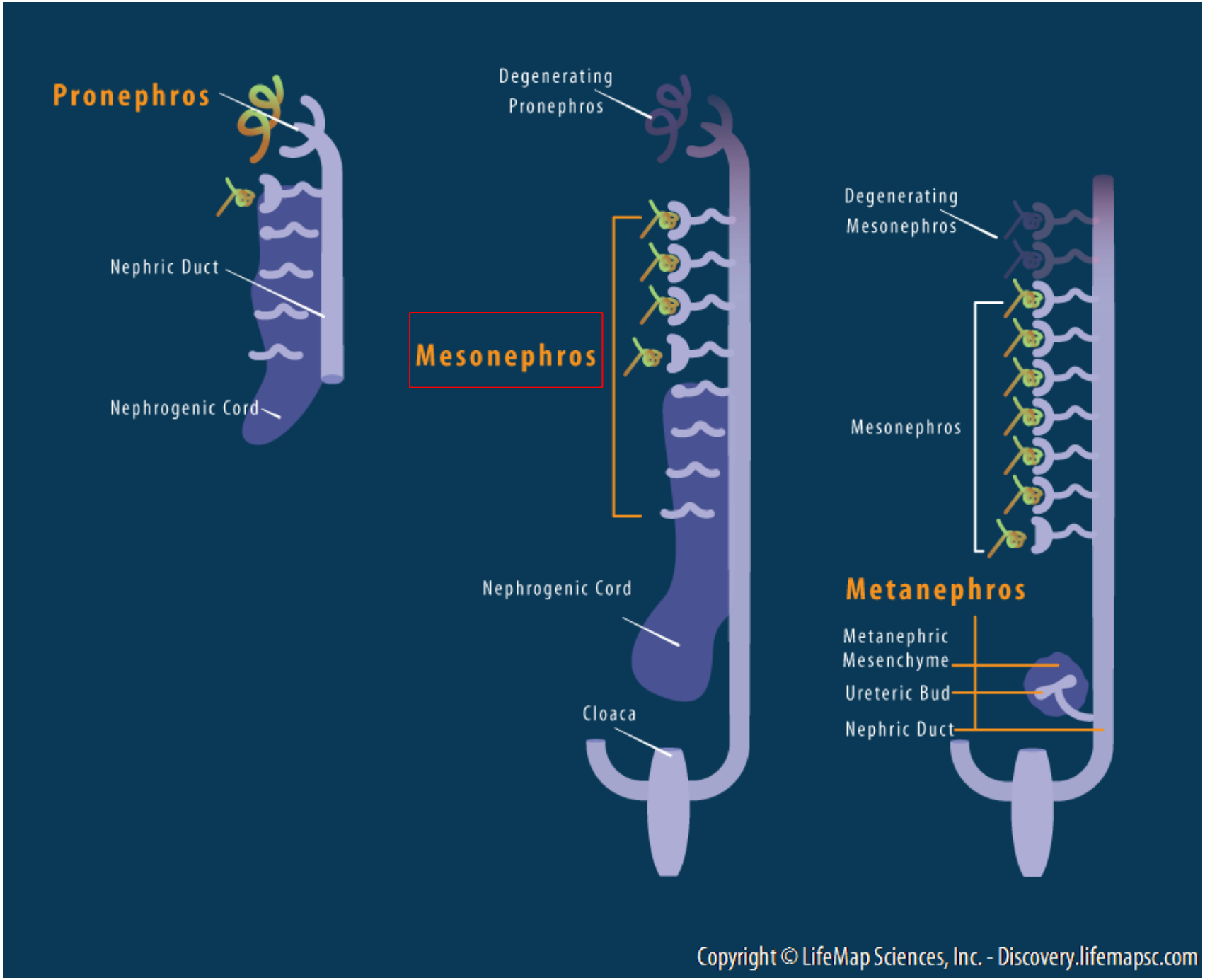
Pronephros (4th week)



Rudimentary primitive glomerular and tubular structures in the neck region, which quickly degenerate

Wolff duct


Pronephros
Nephric Duct
Nephrogenic Cord
Degenerating
Pronephros
Mesonephros
Nephrogenic Cord
Cloaca
Degenerating
Mesonephros
Mesonephros
Metanephros
Metanephric
Mesenchyme
Ureteric Bud
Nephric Duct
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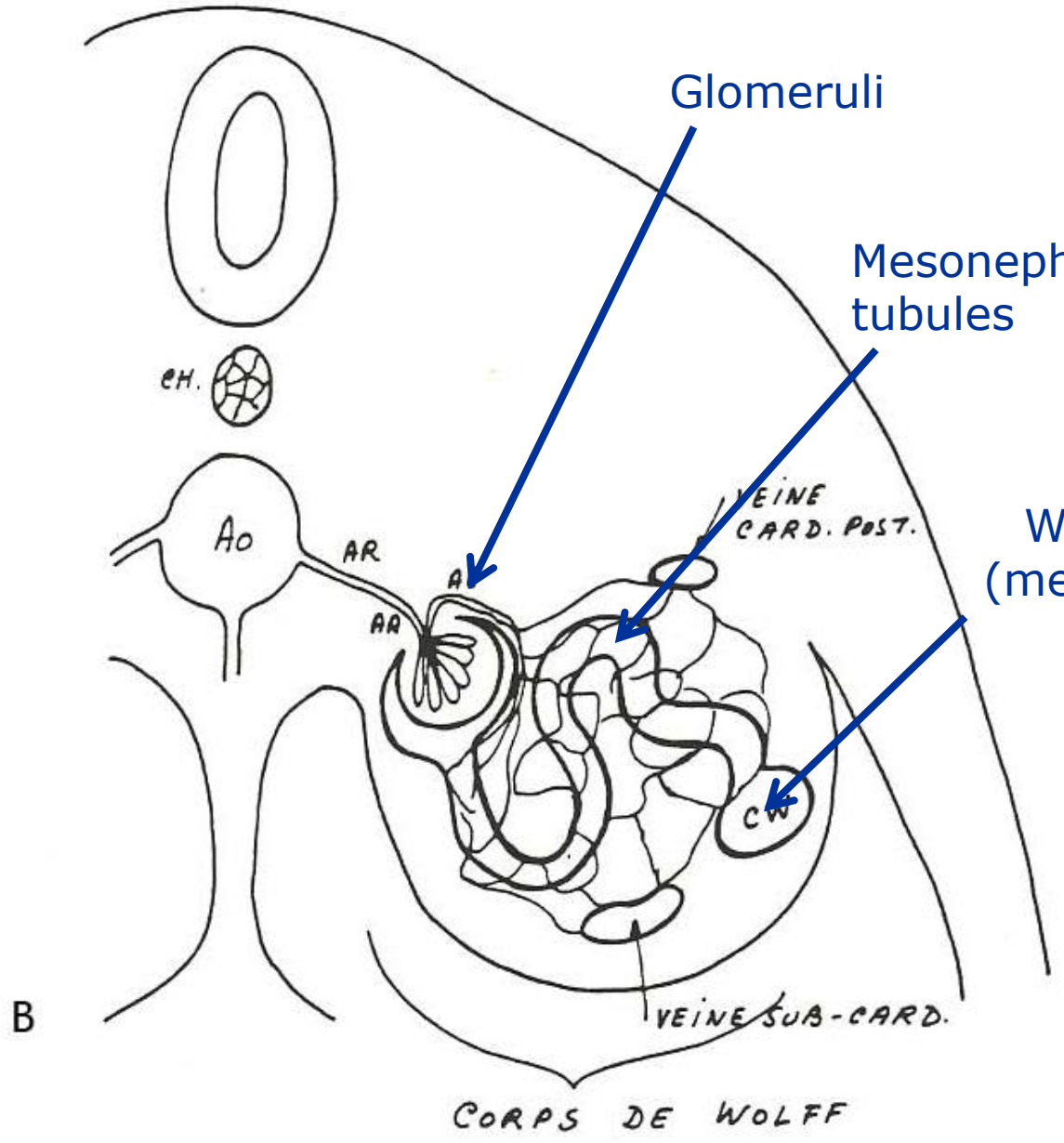
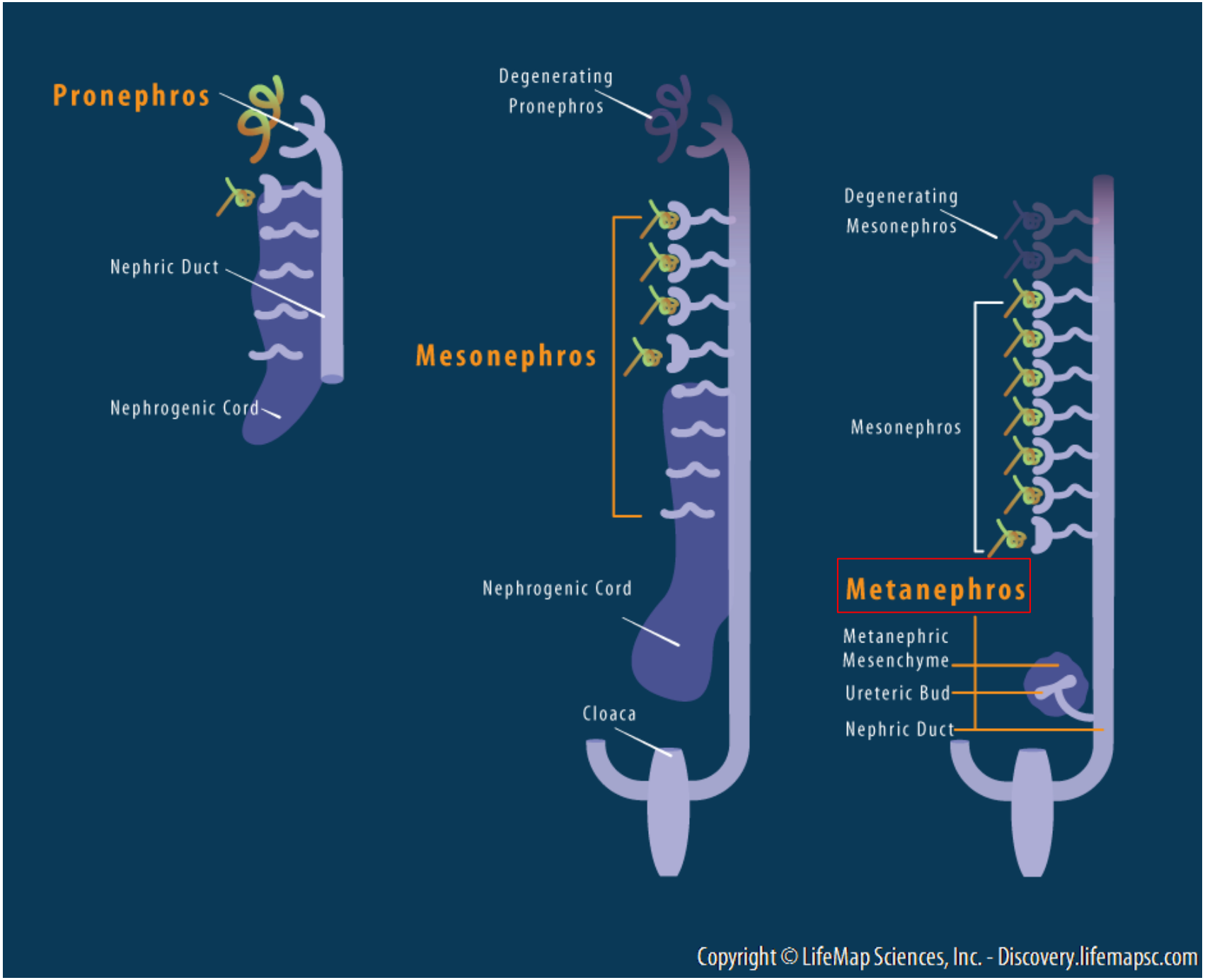
Mesonephros (4-5th weeks) = interim kidney




Pronephros
Nephric Duct
Nephrogenic Cord
Degenerating
Pronephros
Mesonephros
Nephrogenic Cord
Cloaca
Degenerating
Mesonephros
Mesonephros
Metanephros
Metanephric
Mesenchyme
Ureteric Bud
Nephric Duct
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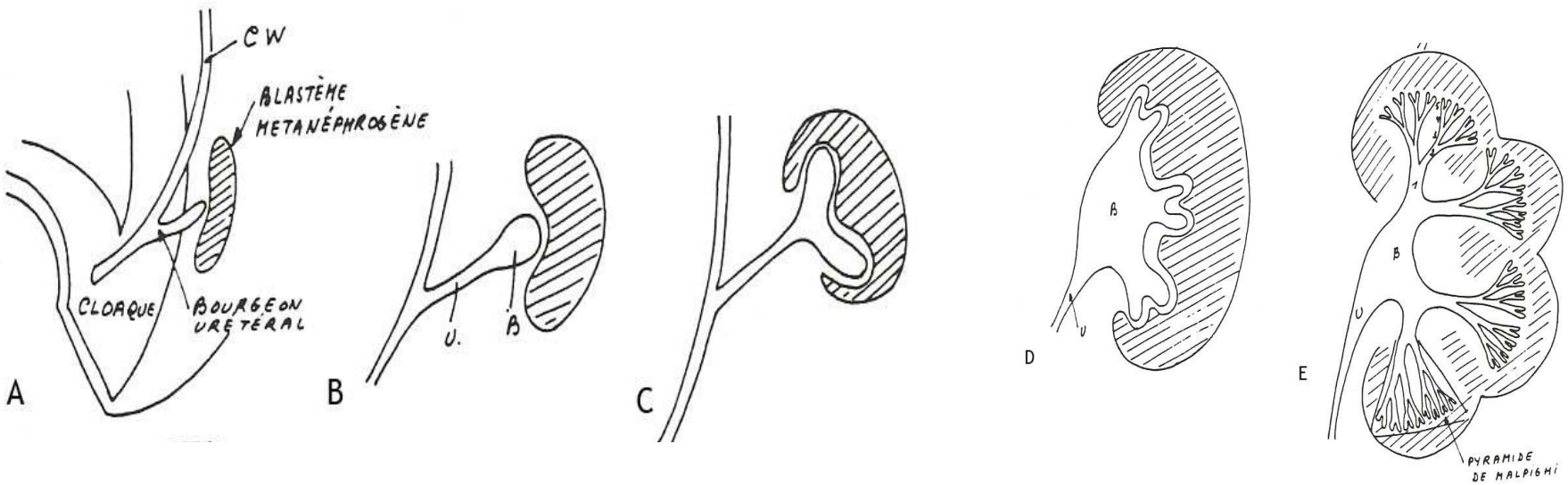
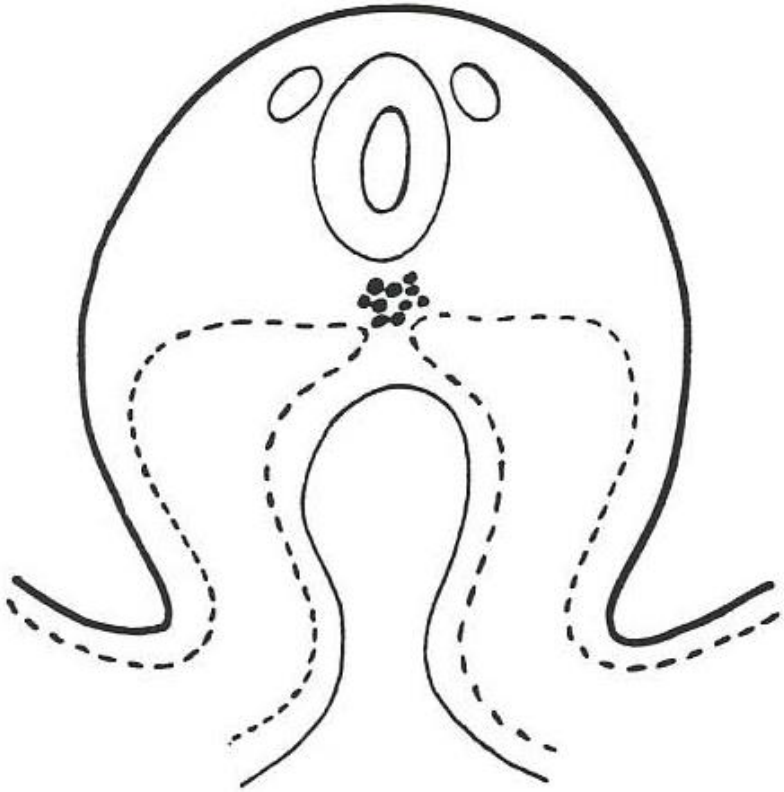
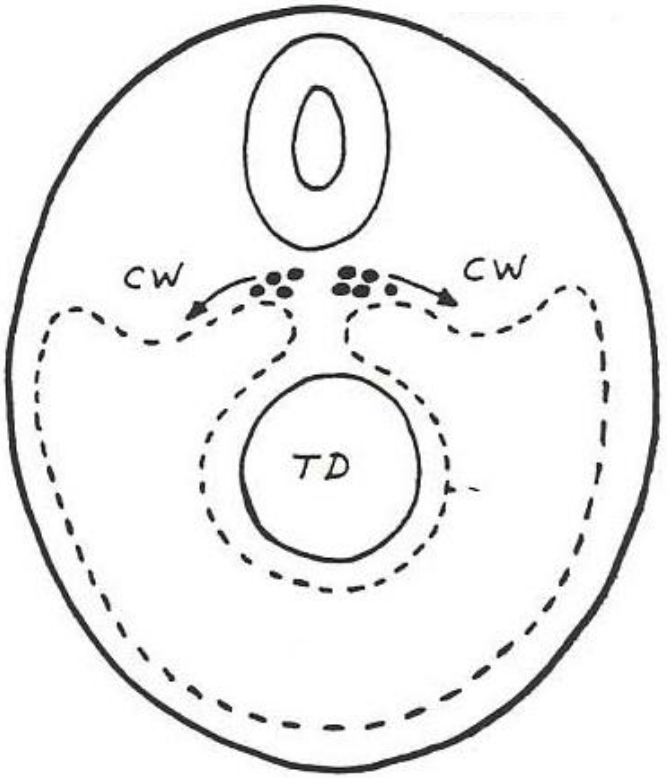
Metanephros (5-8th weeks) = permanent kidney



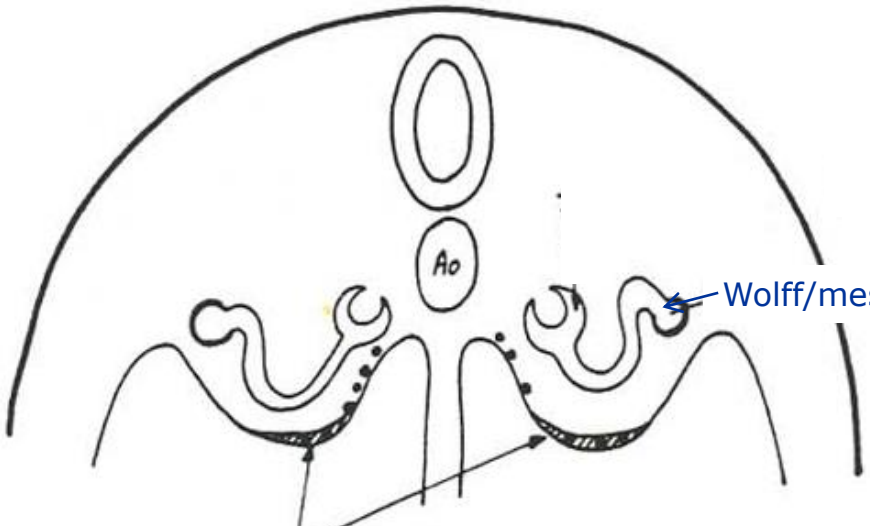
Gonadal differentiation

Migration of the primordial germ cells into the **mesonephros** (5th week)





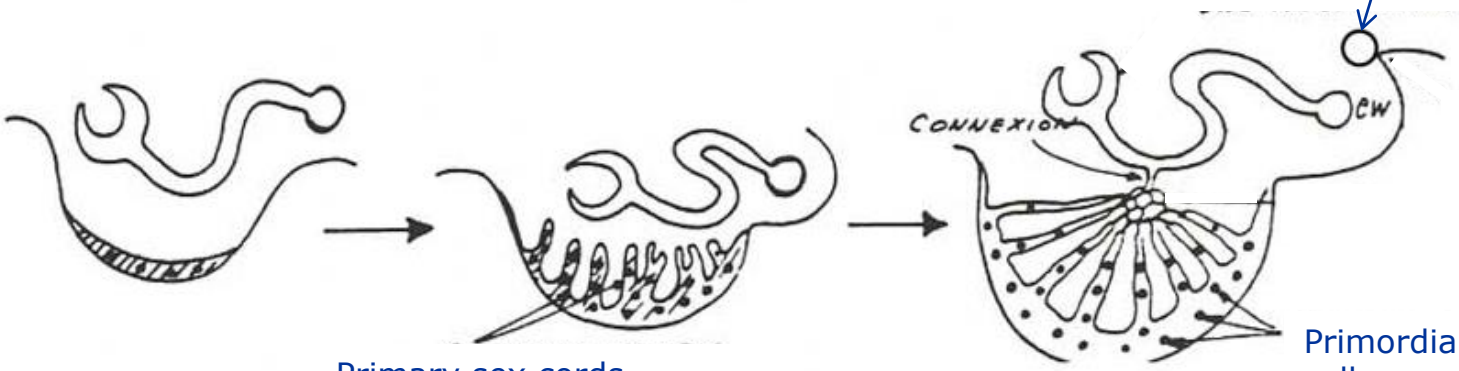
Indifferent gonads (5th week)



Wolff/mesonephric duct (cw)

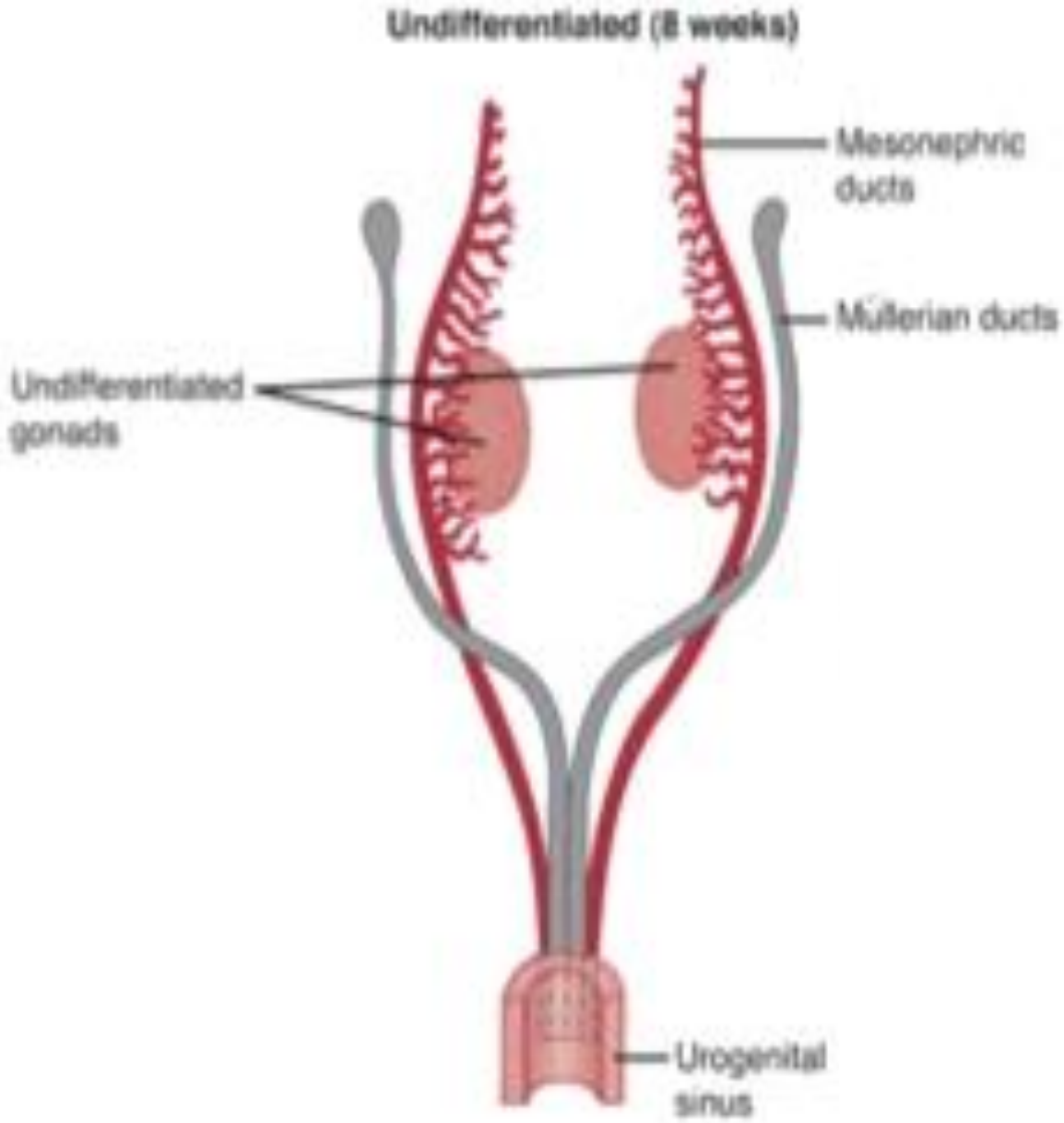
Mullerian duct
(paramesonephric duct)

Gonadal ridges

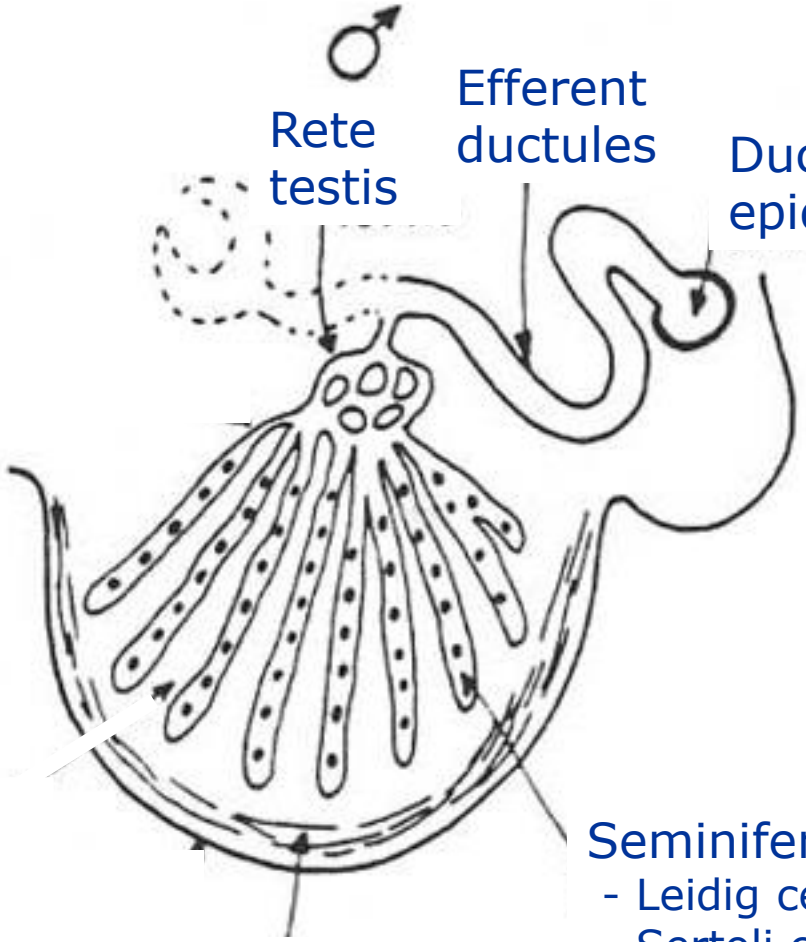


Primary sex cords

Primordial germ cells

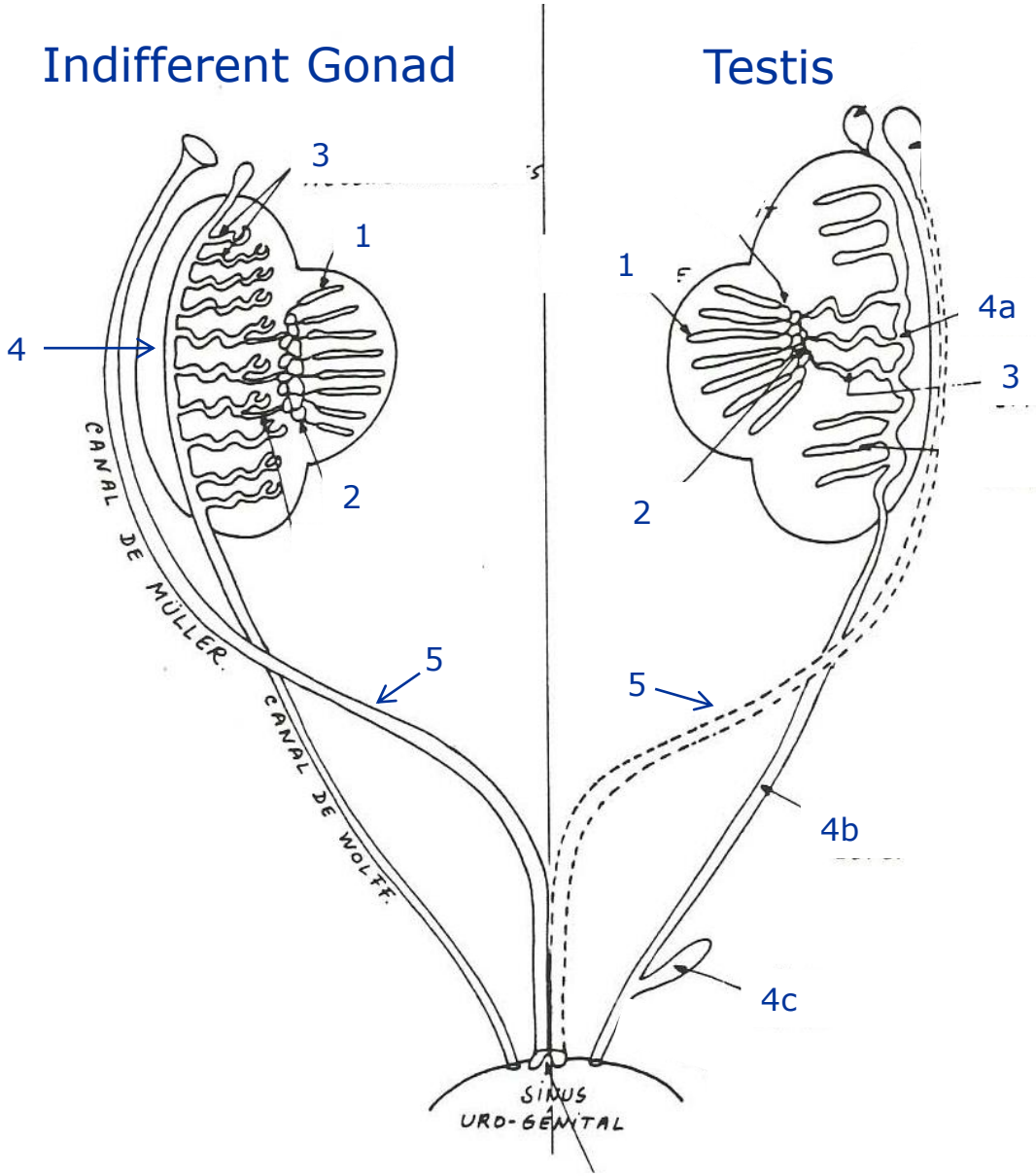

Undifferentiated (8 weeks)
Mesonephric ducts
Müllerian ducts
Undifferentiated gonads
Urogenital sinus

Development of testes (7th week)



ABP: Androgen Binding Protein
MIS: Mullerian inhibiting substance

Development of testes (7th week)



1. Primary sex cords
> seminifereous tubules

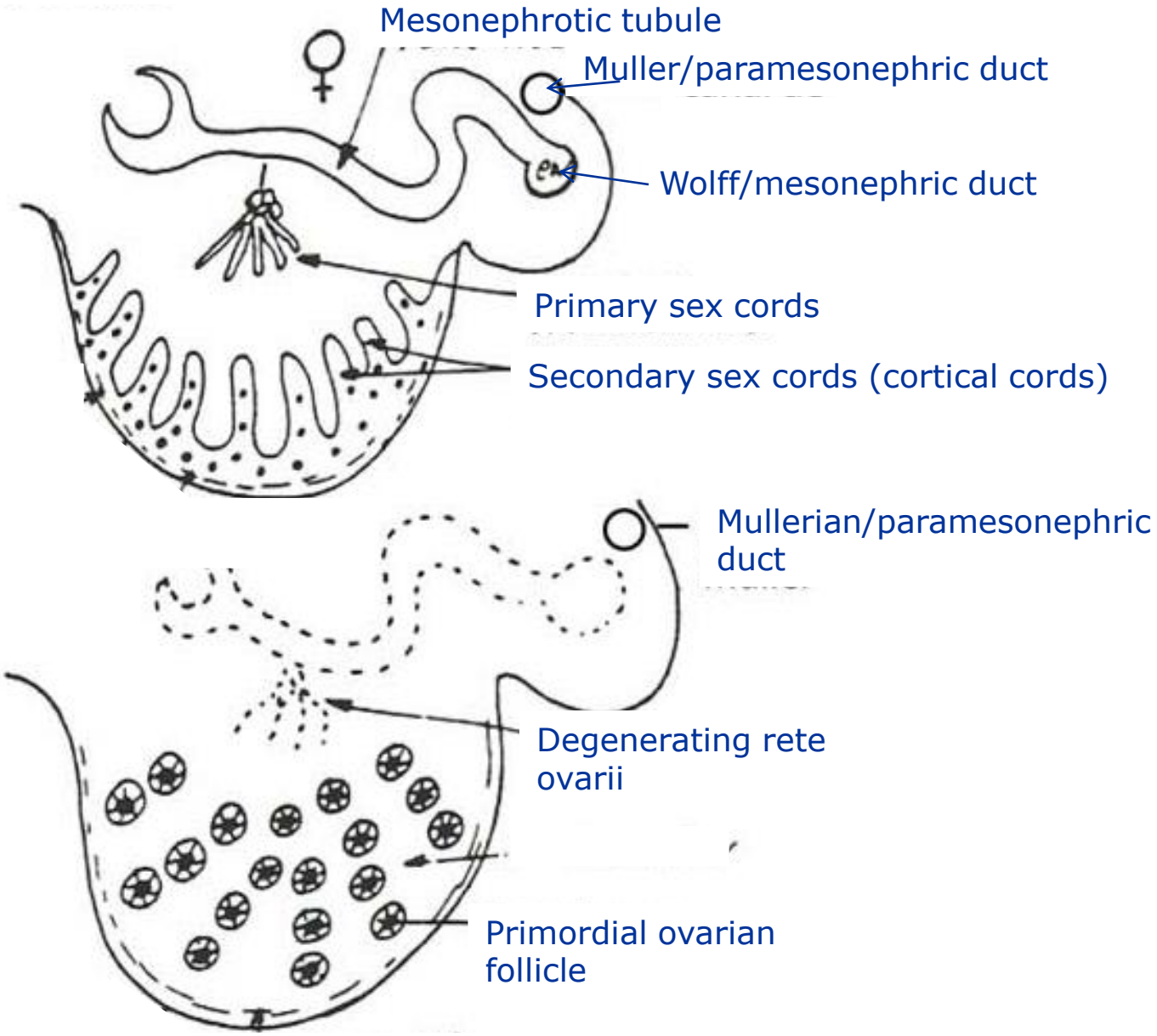
2. Rete > rete testis

3. Mesonephric tubules
> efferent ductules

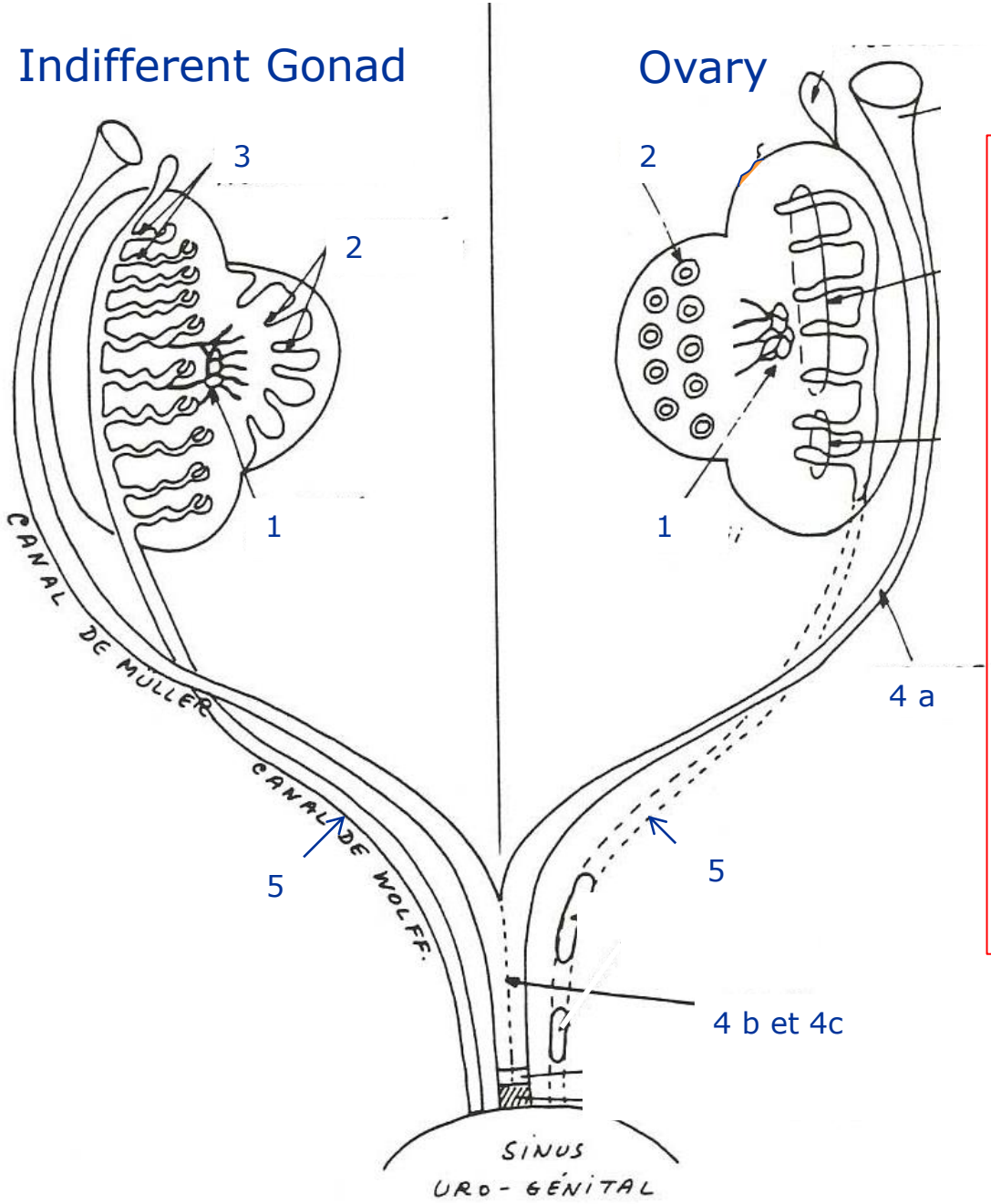
4. Wolff/Mesonephric duct
> ductus epididymis (a)
> vas deferens (b)
> seminal vesicle (c)

5. Mullerian/paramesonephric duct: degenerates (MIS)

Development of ovaries (10th week)



Development of ovaries (10th week)



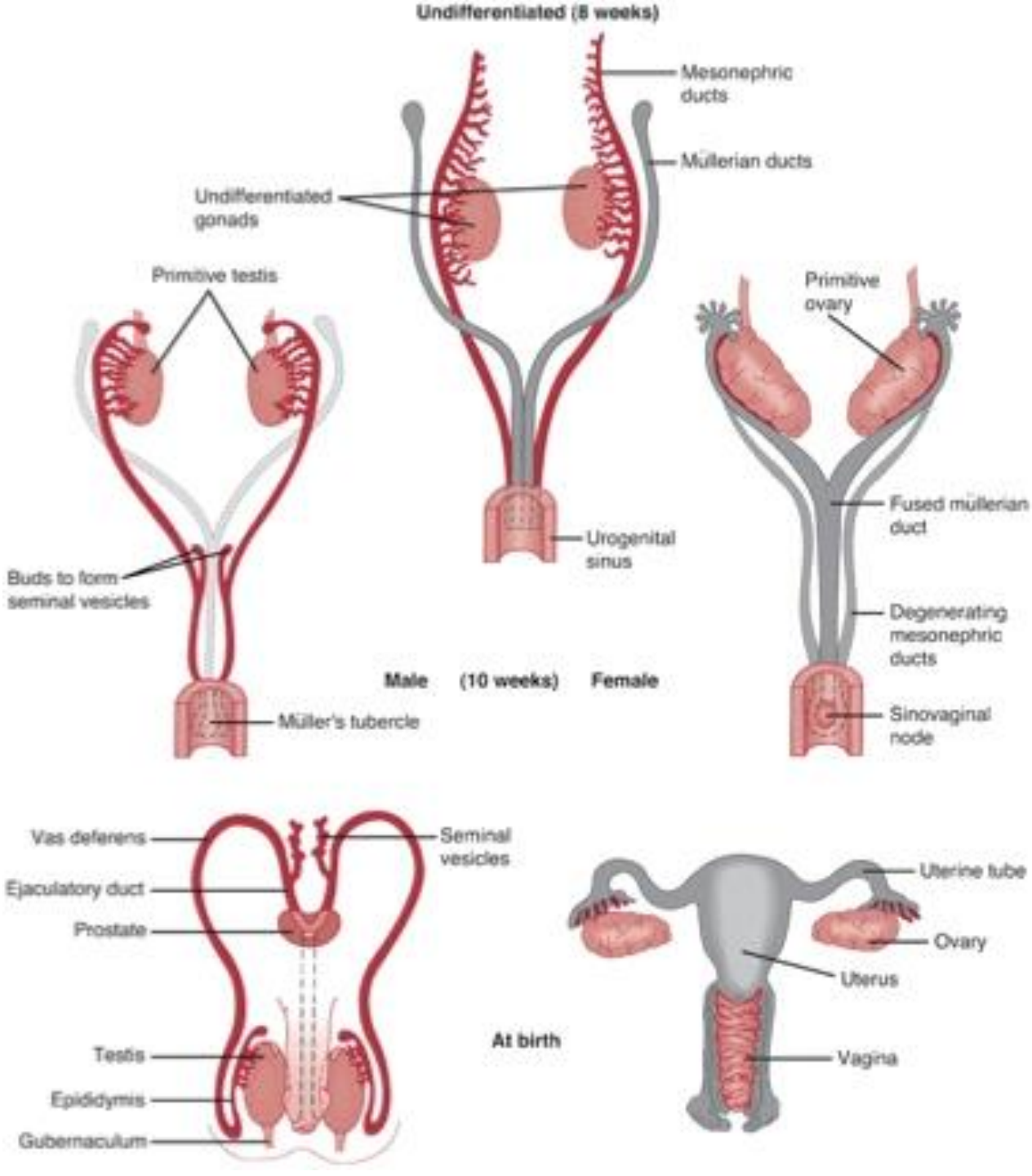
1. Primary sex cords
> rete ovarii

2. Secondary sex cords
> primordial follicles

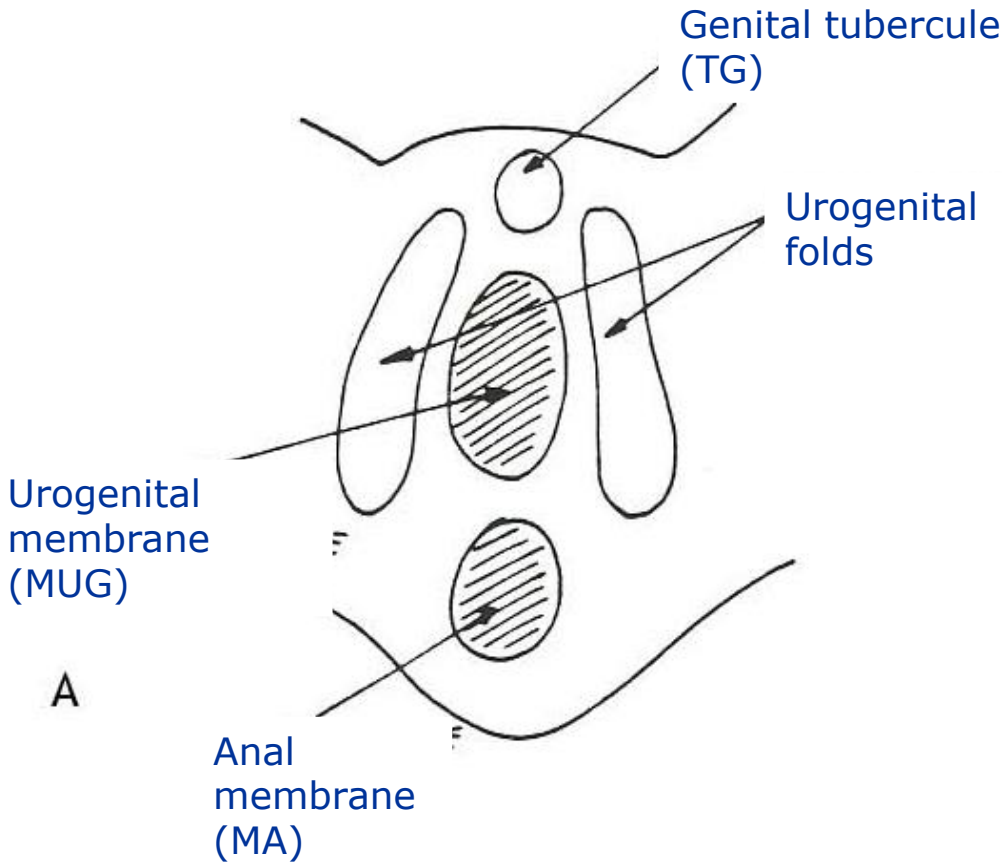
3. Mesonephric tubules degenerate

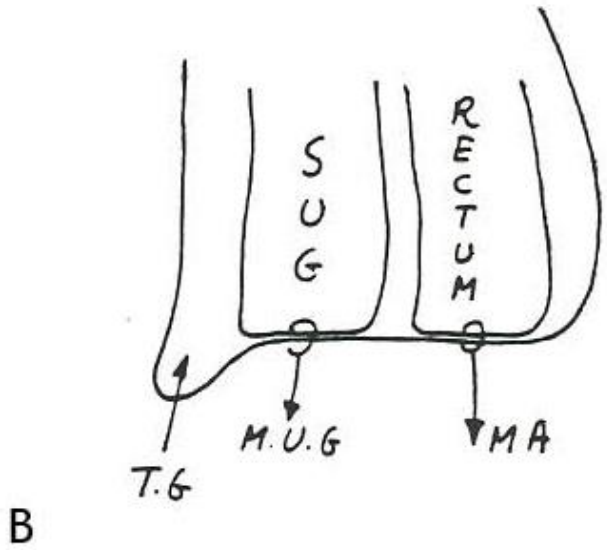
4. Mullerian/ paramesonephric duct
> Fallopian tubes(a)
> uterus (b)
> upper vagina(c)

5. Wolff/mesonephric duct: degenerates

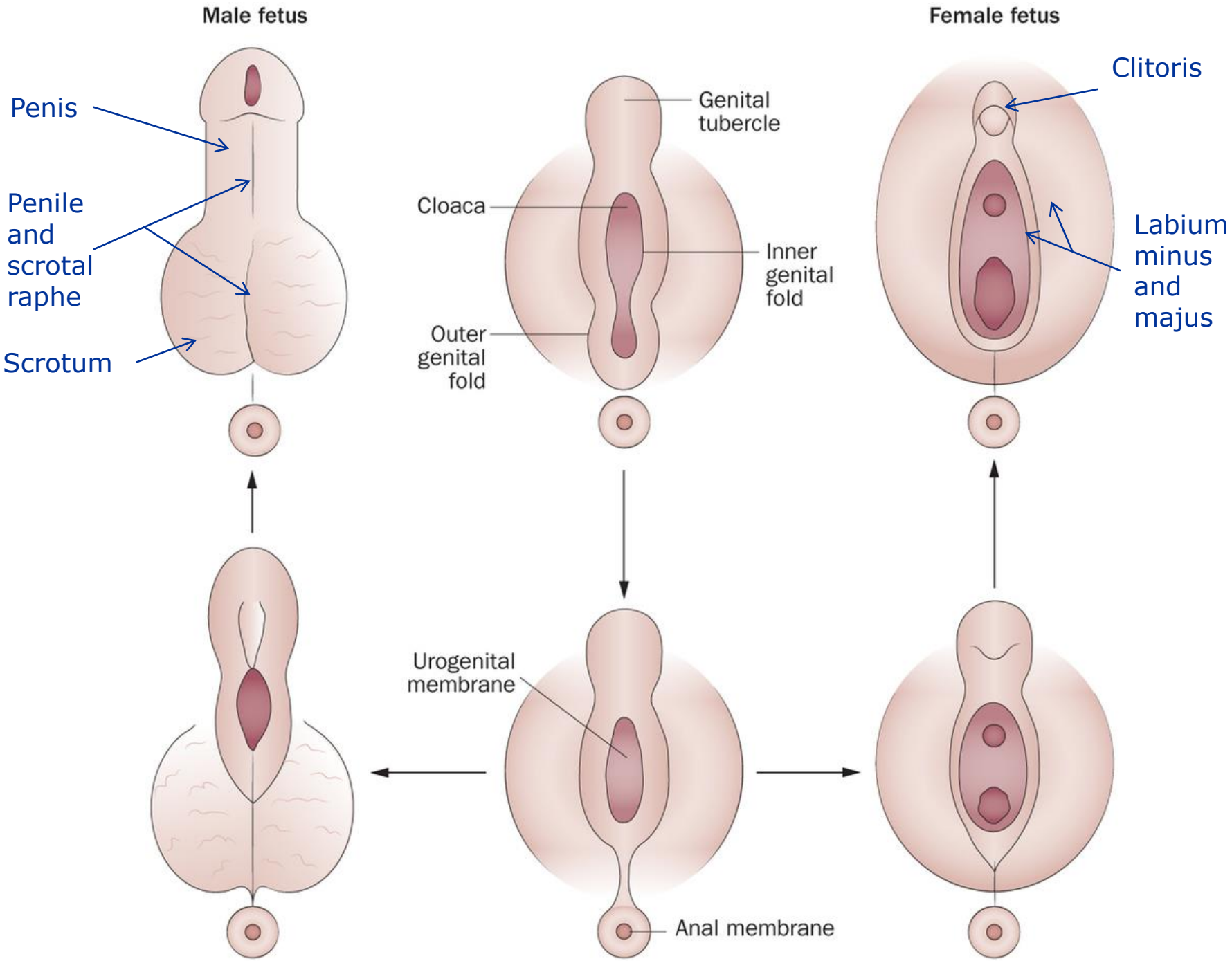

Undifferentiated (8 weeks)
Mesonephric ducts
Müllerian ducts
Undifferentiated gonads
Primitive testis
Primitive ovary
Urogenital sinus
Buds to form seminal vesicles
Fused müllerian duct
Degenerating mesonephric ducts
Male (10 weeks) Female
Müller's tubercle
Sinovaginal node
Vas deferens
Seminal vesicles
Ejaculatory duct
Prostate
Uterine tube
Ovary
Uterus
At birth
Testis
Epididymis
Vagina
Gubernaculum

External Genitalia

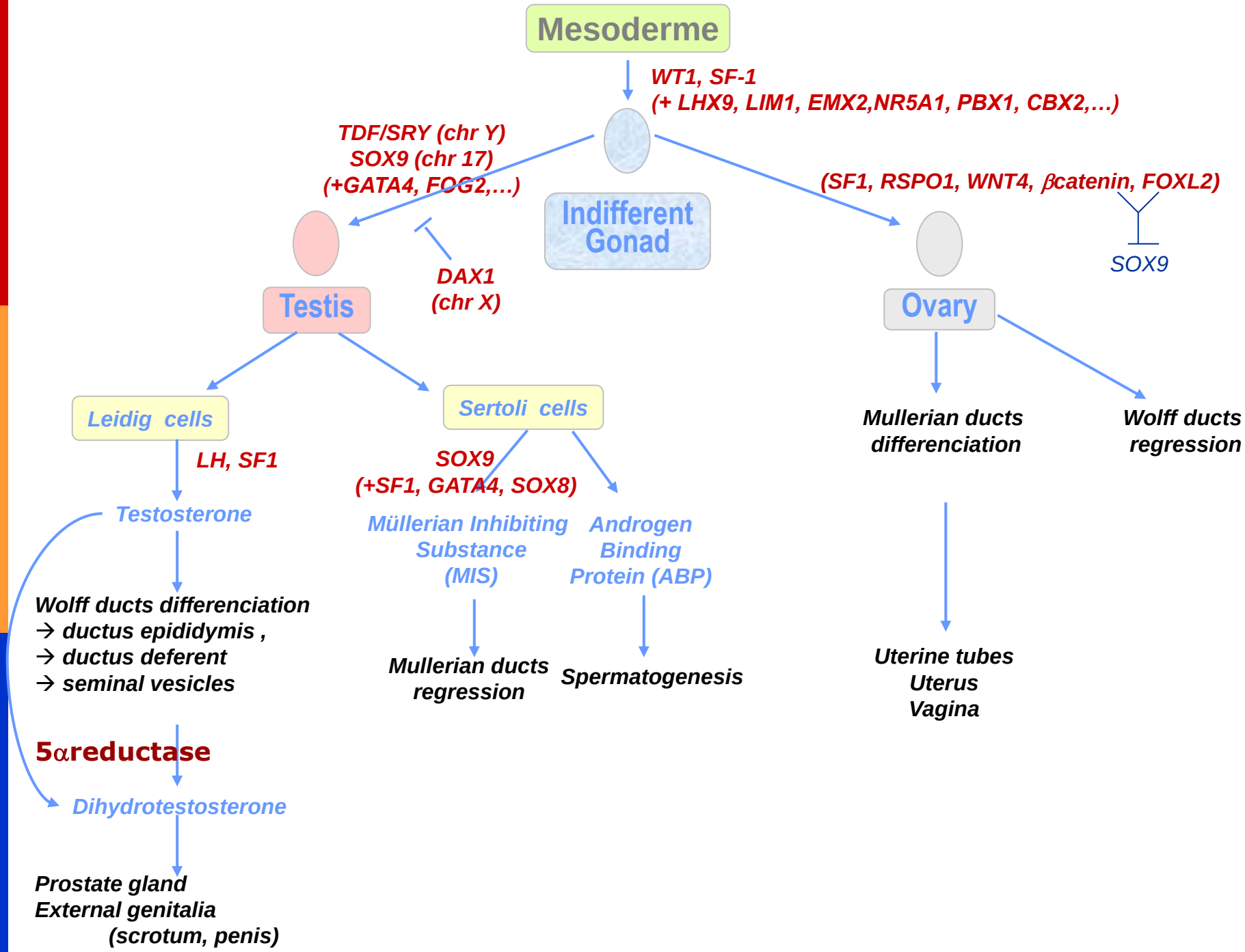


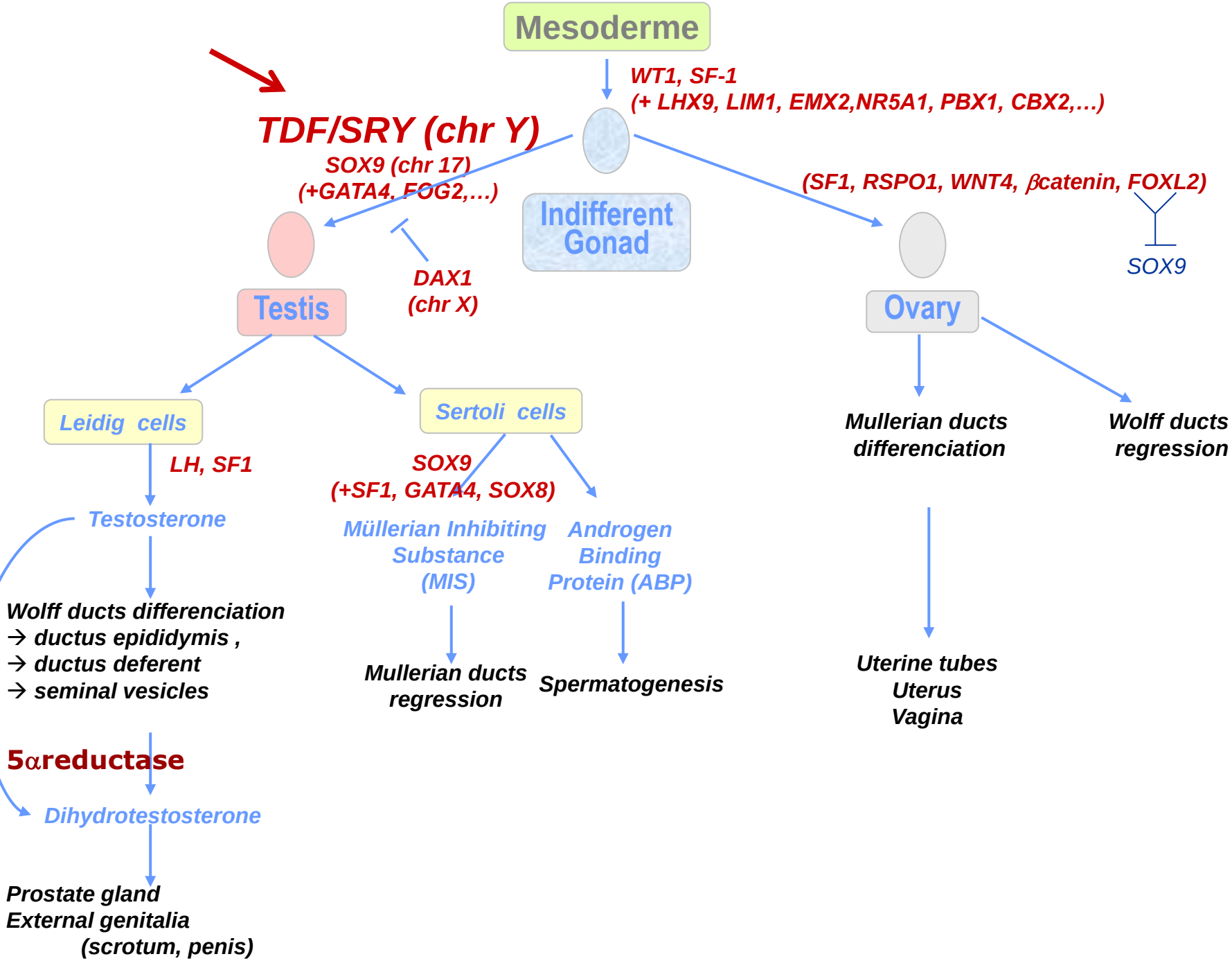


SUG: Urogenital sinus


Male fetus
Female fetus
Penis
Penile and scrotal raphe
Scrotum
Genital tubercle
Cloaca
Inner genital fold
Outer genital fold
Clitoris
Labium minus and majus
Urogenital membrane
Anal membrane

BIOLOGY OF GENITAL DIFFERENTIATION


Mesoderme
WT1, SF-1
(+ LHX9, LIM1, EMX2,NR5A1, PBX1, CBX2,…)
TDF/SRY (chr Y)
SOX9 (chr 17)
(+GATA4, FOG2,…)
(SF1, RSPO1, WNT4, βcatenin, FOXL2)
Indifferent Gonad
SOX9
DAX1
(chr X)
Testis
Ovary
Leidig cells
Sertoli cells
Mullerian ducts differenciation
Wolff ducts regression
LH, SF1
SOX9
(+SF1, GATA4, SOX8)
Testosterone
Müllerian Inhibiting Substance (MIS)
Androgen Binding Protein (ABP)
Wolff ducts differenciation
→ ductus epididymis ,
→ ductus deferent
→ seminal vesicles
Mullerian ducts regression
Spermatogenesis
Uterine tubes
Uterus
Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)


Mesoderme
WT1, SF-1
(+ LHX9, LIM1, EMX2,NR5A1, PBX1, CBX2,…)
TDF/SRY (chr Y)
SOX9 (chr 17)
(+GATA4, FOG2,…)
Indifferent Gonad
(SF1, RSPO1, WNT4, βcatenin, FOXL2)
SOX9
DAX1
(chr X)
Testis
Ovary
Leidig cells
Sertoli cells
LH, SF1
SOX9
(+SF1, GATA4, SOX8)
Testosterone
Müllerian Inhibiting Substance (MIS)
Androgen Binding Protein (ABP)
Mullerian ducts differenciation
Wolff ducts regression
Wolff ducts differenciation
→ ductus epididymis ,
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→ seminal vesicles
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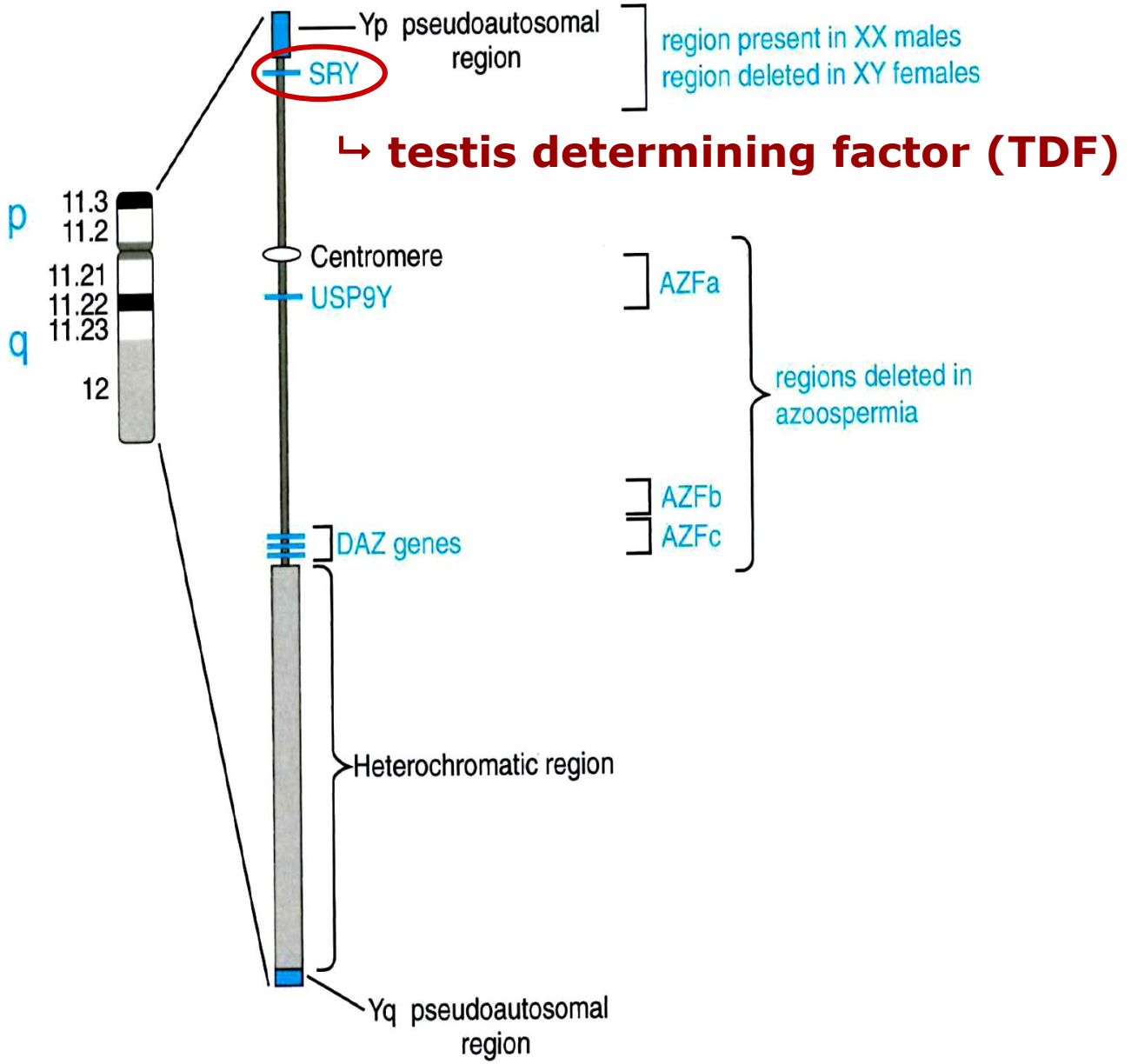
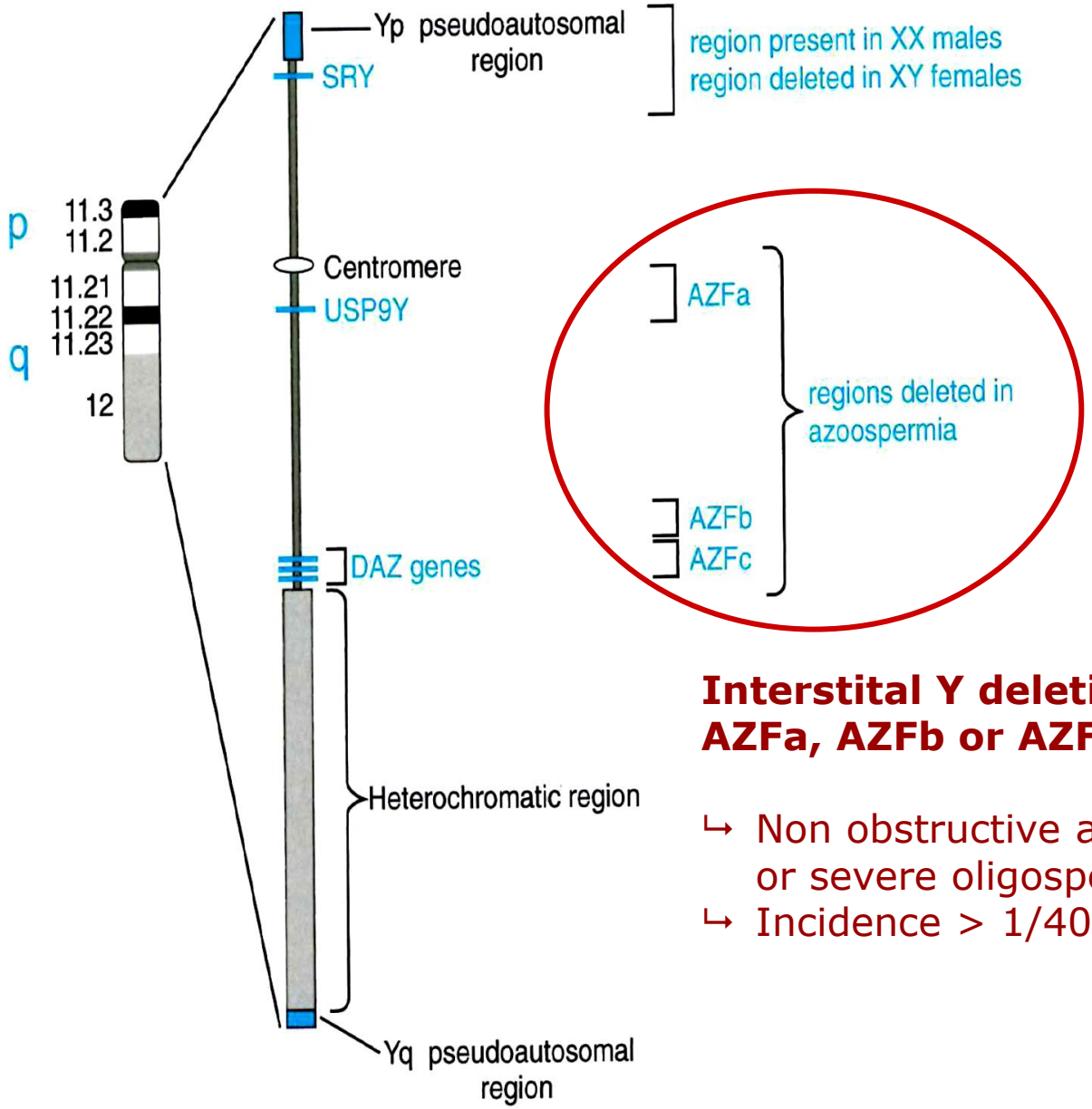
Spermatogenesis
Uterine tubes
Uterus
Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

The Y chromosome



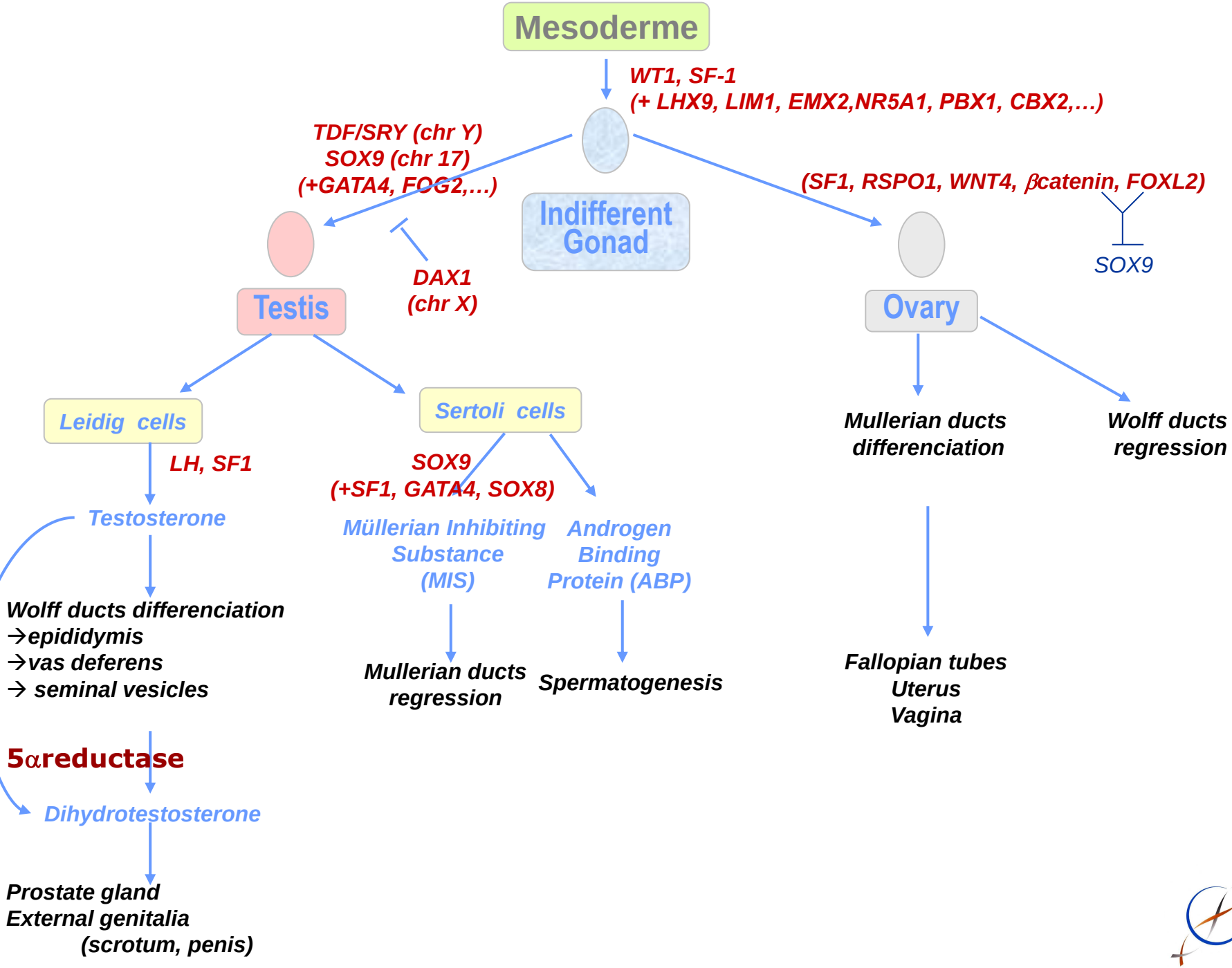
The Y chromosome



Interstital Y deletion including AZFa, AZFb or AZFc

- ↳ Non obstructive azoospermia or severe oligospermia
- ↳ Incidence > 1/4000

IPG


Mesoderme
WT1, SF-1
(+ LHX9, LIM1, EMX2,NR5A1, PBX1, CBX2,…)
TDF/SRY (chr Y)
SOX9 (chr 17)
(+GATA4, FOG2,…)
Indifferent Gonad
(SF1, RSPO1, WNT4, βcatenin, FOXL2)
SOX9
DAX1
(chr X)
Testis
Ovary
Leidig cells
Sertoli cells
Mullerian ducts differenciation
Wolff ducts regression
LH, SF1
SOX9
(+SF1, GATA4, SOX8)
Testosterone
Müllerian Inhibiting Substance (MIS)
Androgen Binding Protein (ABP)
Wolff ducts differenciation
→epididymis
→vas deferens
→ seminal vesicles
Mullerian ducts regression
Spermatogenesis
Fallopian tubes
Uterus
Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

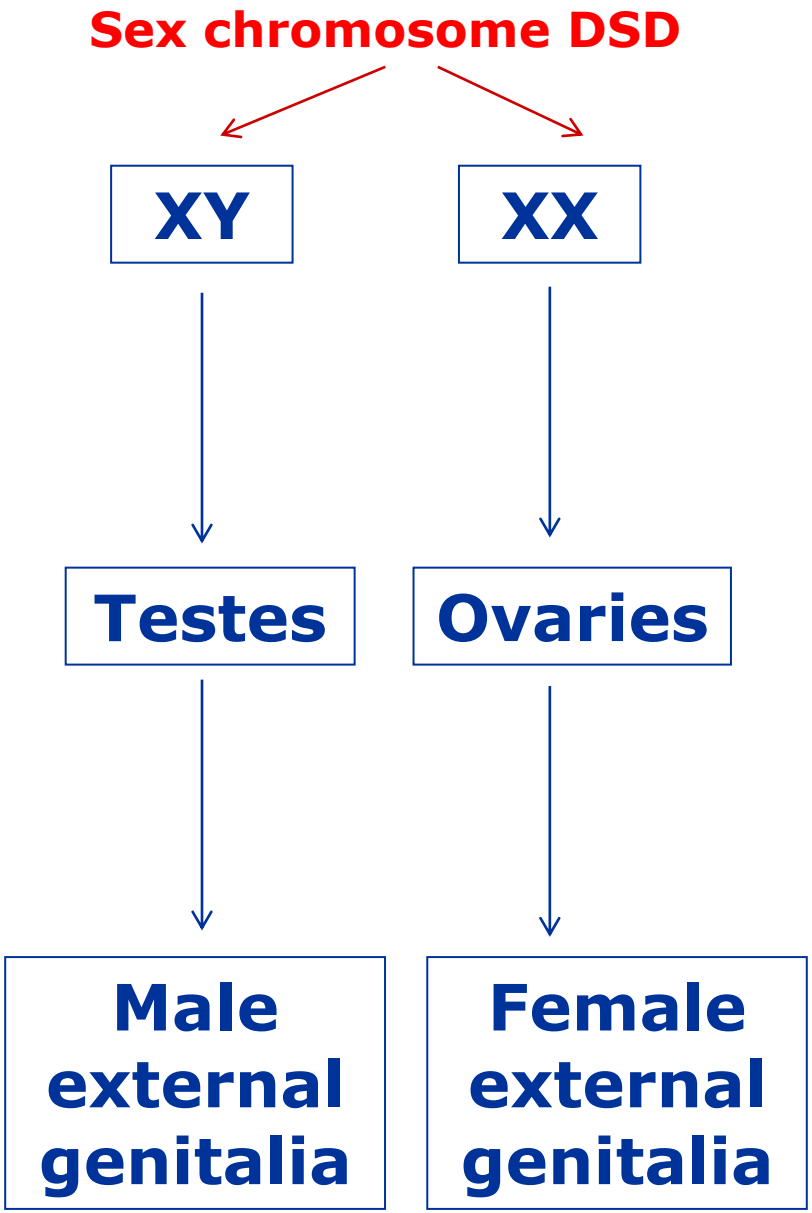
DSD: DISORDERS OF SEXUAL DEVELOPMENT

DEFINITIONS:

- GENETIC SEX: XX or XY

- GONADAL SEX: Ovaries or testes

- PHENOTYPICAL SEX: Male or female external genitalia


Sex chromosome DSD
XY
XX
Testes
Ovaries
Male external genitalia
Female external genitalia

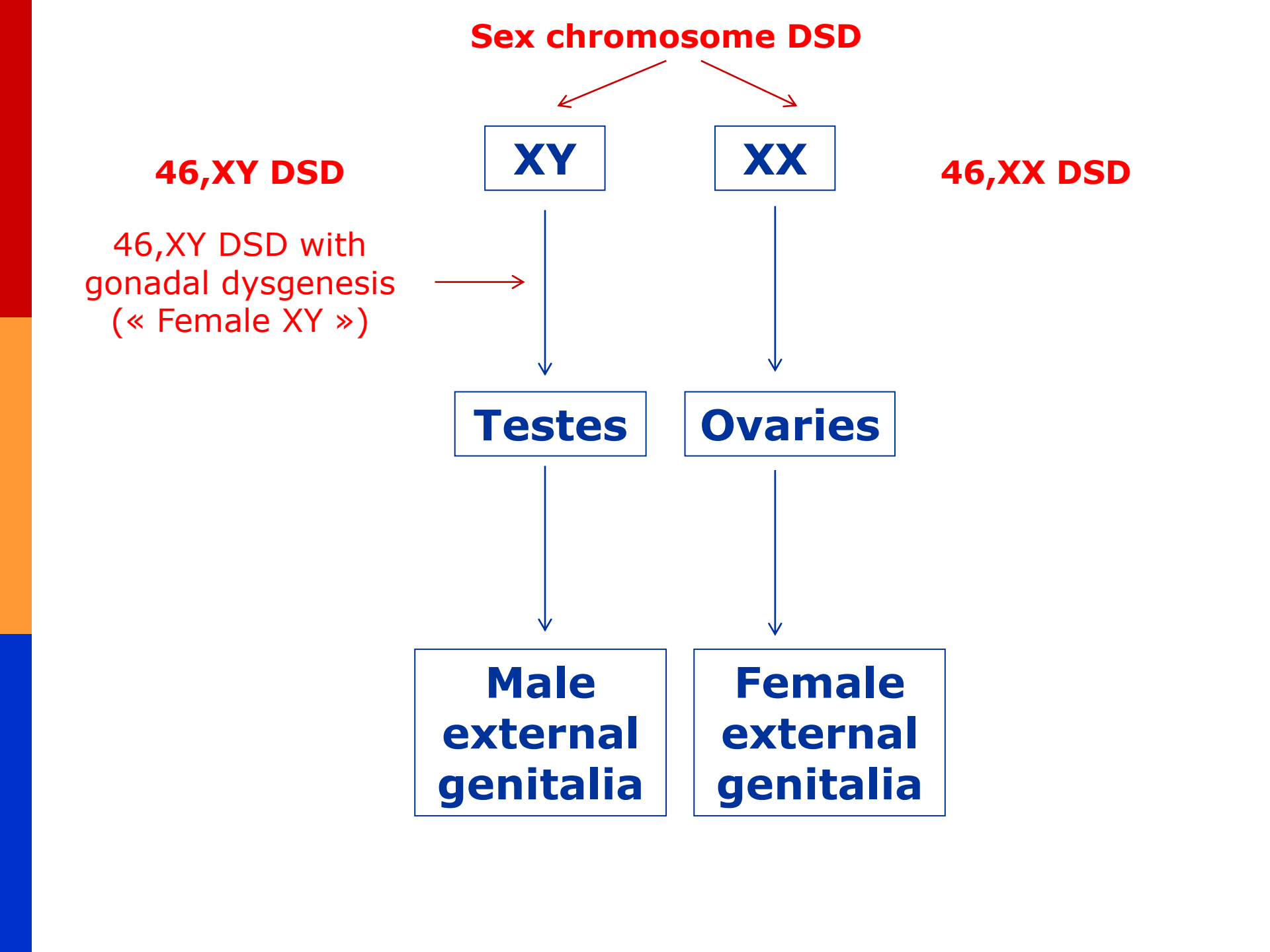
1. **Sex chromosome DSD**

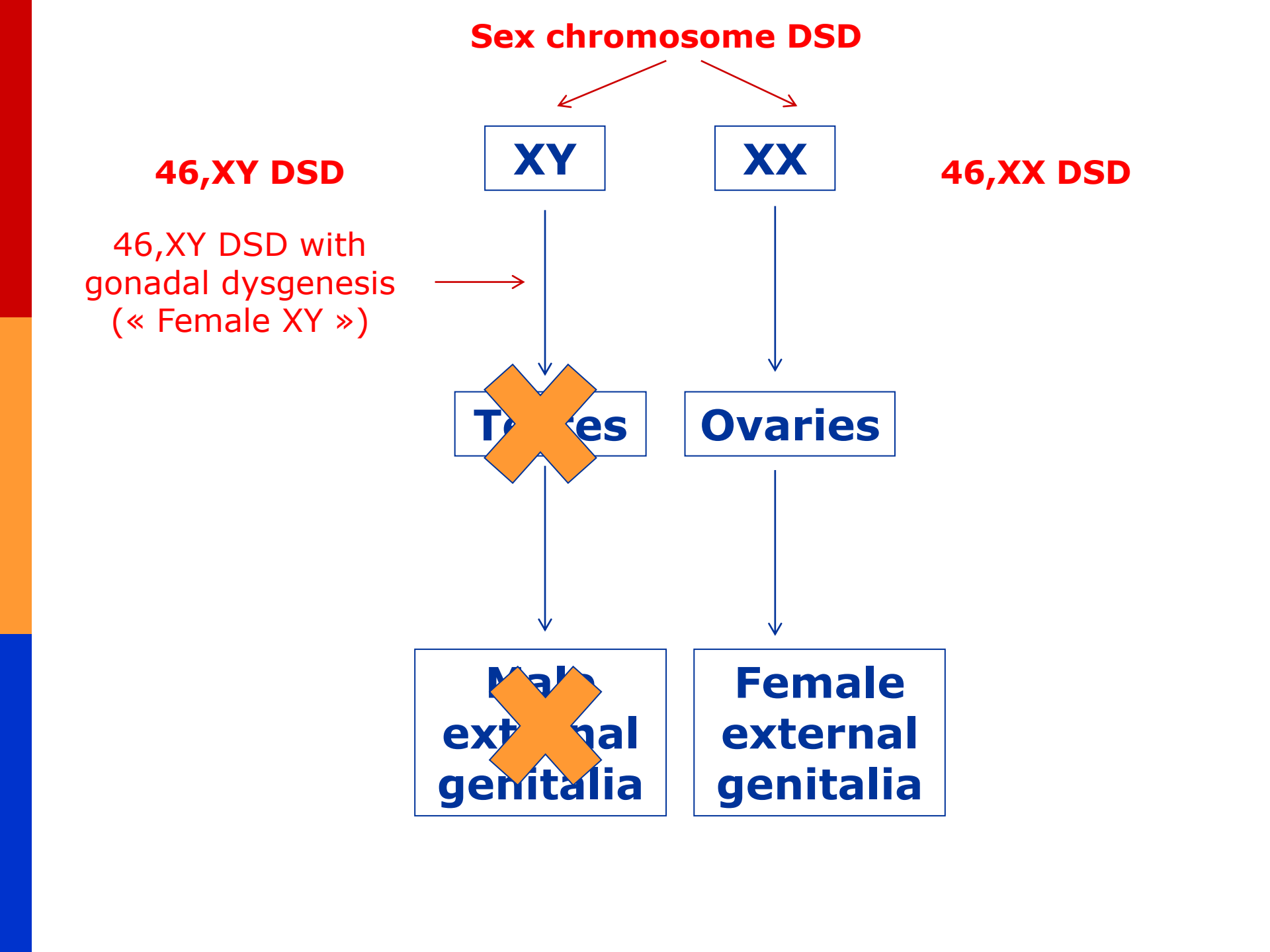
    1.1. Ovotesticular DSD

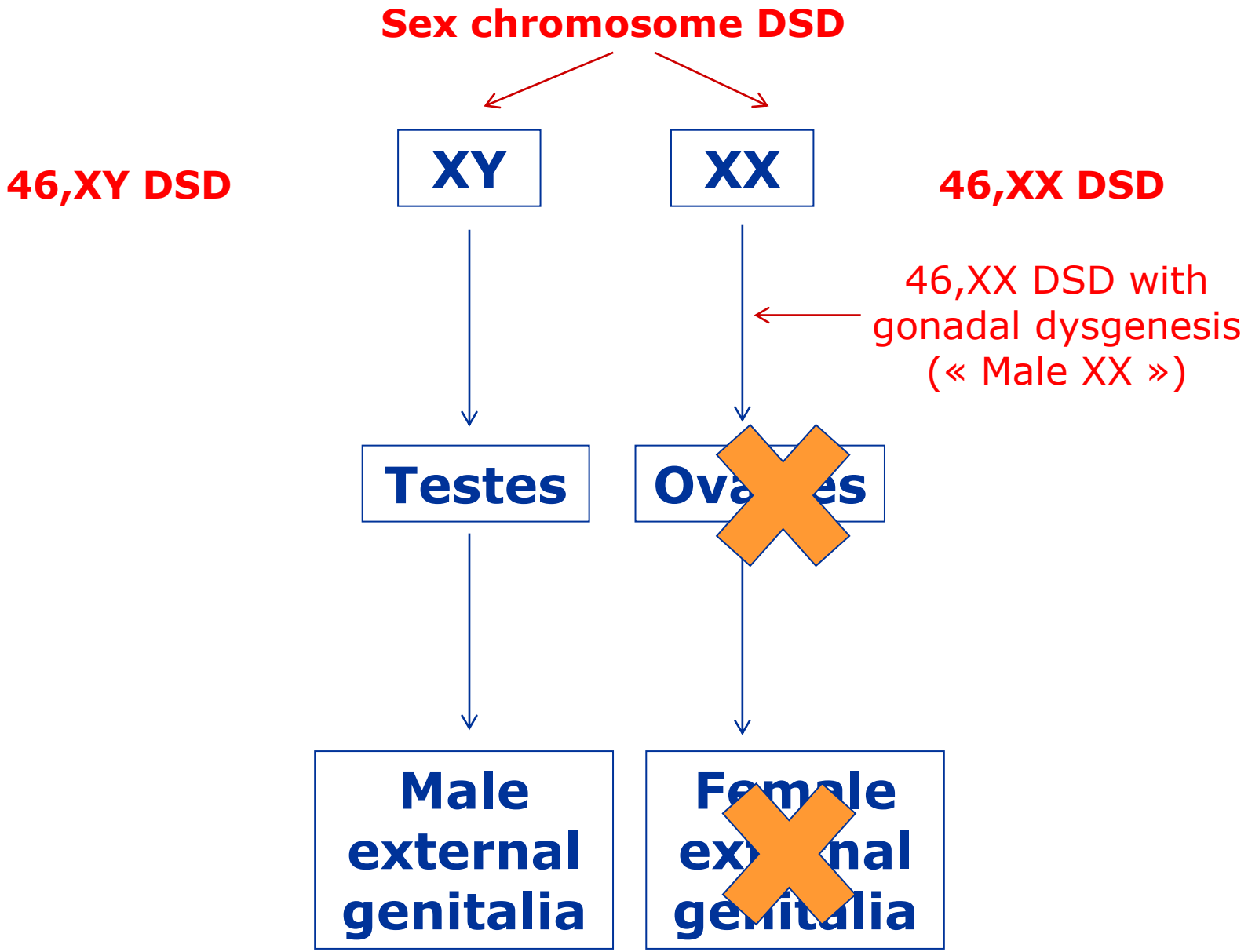
    1.2. 45,X and Turner variants

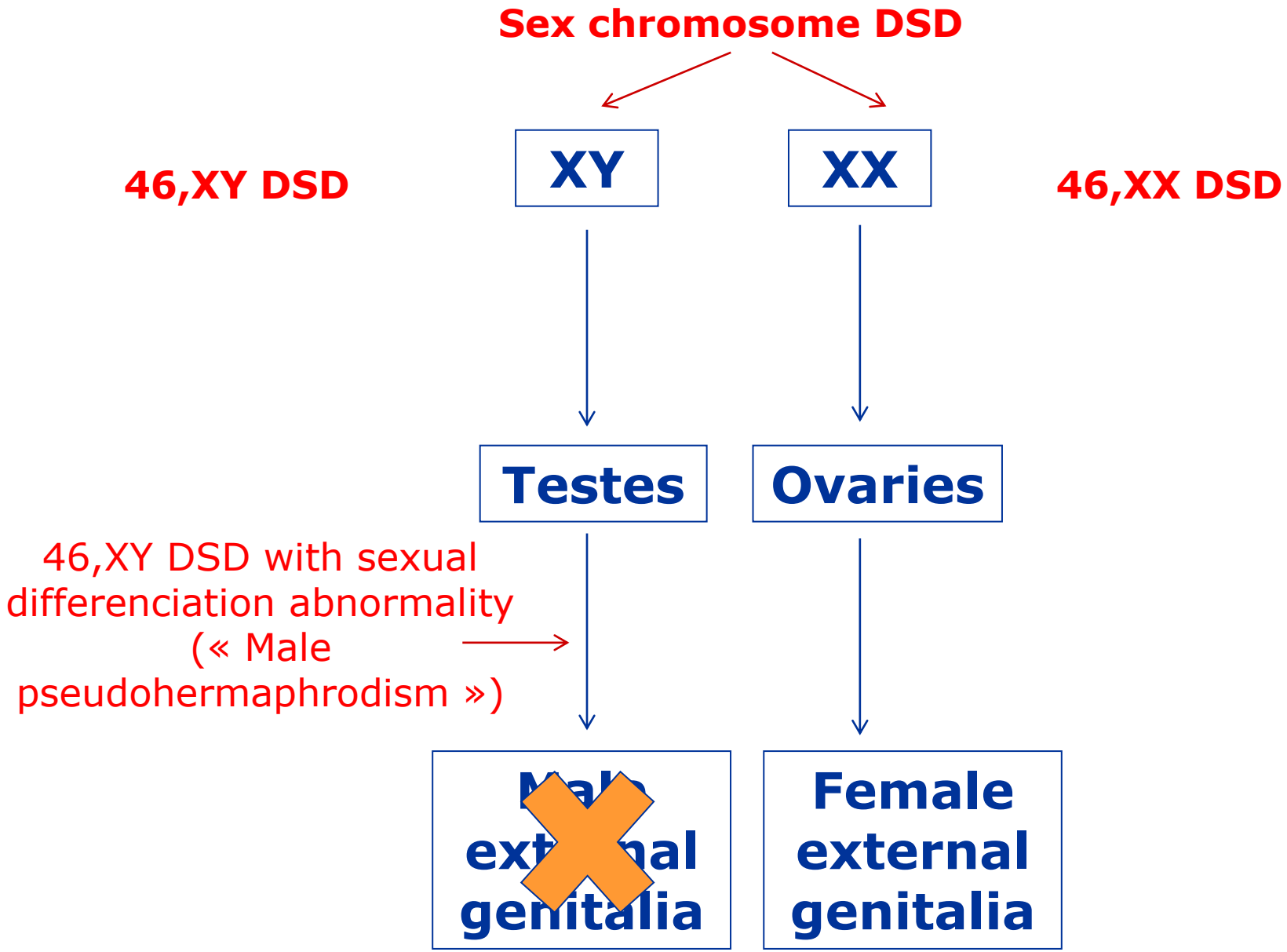
    1.3. 47,XXY and Klinefelter variants

    1.4. 45,X/46,XY mixed gonadal dysgenesis (MGD)


Sex chromosome DSD
XY
XX
46,XY DSD
46,XX DSD
46,XY DSD with gonadal dysgenesis (« Female XY »)
Testes
Ovaries
Male external genitalia
Female external genitalia


Sex chromosome DSD
XY
XX
46,XY DSD
46,XX DSD
46,XY DSD with gonadal dysgenesis (« Female XY »)
Ovaries
Female external genitalia


Sex chromosome DSD
46,XY DSD
XY
XX
46,XX DSD
46,XX DSD with gonadal dysgenesis (« Male XX »)
Testes
Male external genitalia


Sex chromosome DSD
46,XY DSD
XY
XX
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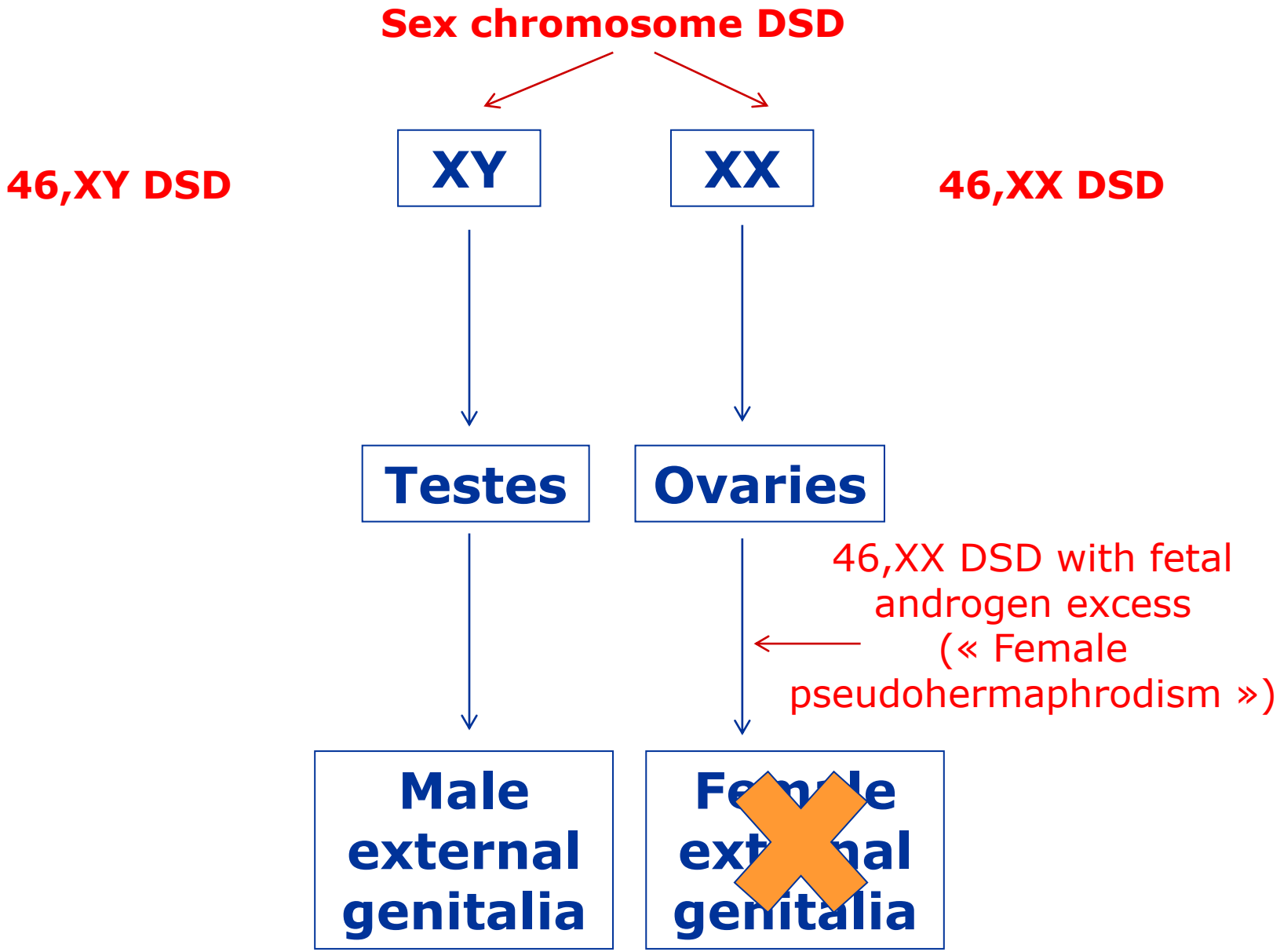
Testes
Ovaries
46,XY DSD with sexual differenciation abnormality (« Male pseudohermaphrodism »)
Female external genitalia


Sex chromosome DSD
46,XY DSD
XY
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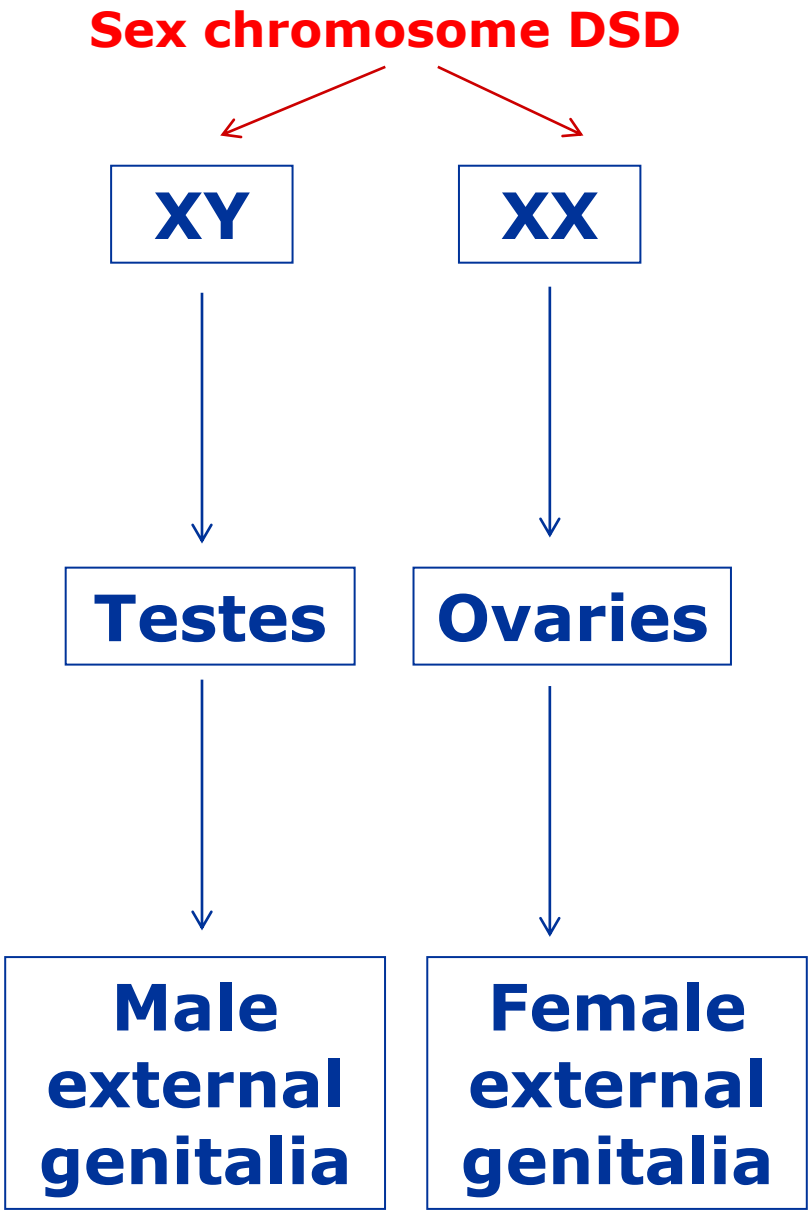
46,XX DSD
Testes
Ovaries
46,XX DSD with fetal androgen excess (« Female pseudohermaphrodism »)
Male external genitalia
Female external genitalia

1. **Sex chromosome DSD**
    - 1.1. Ovotesticular DSD
    - 1.2. 45,X and Turner variants
    - 1.3. 47,XXY and Klinefelter variants
    - 1.4. 45,X/46,XY mixed gonadal dysgenesis (MGD)

2. **46,XY DSD**
    - 2.1. 46,XY DSD with gonadal dysgenesis
    - 2.2. 46,XY DSD with sexual differenciation abnormality

3. **46,XX DSD**
    - 3.1. 46,XX DSD with gonadal dysgenesis
    - 3.2. 46,XX DSD with fetal androgen excess

Sex chromosome DSD


Sex chromosome DSD
XY
XX
Testes
Ovaries
Male external genitalia
Female external genitalia

1. Ovotesticular DSD

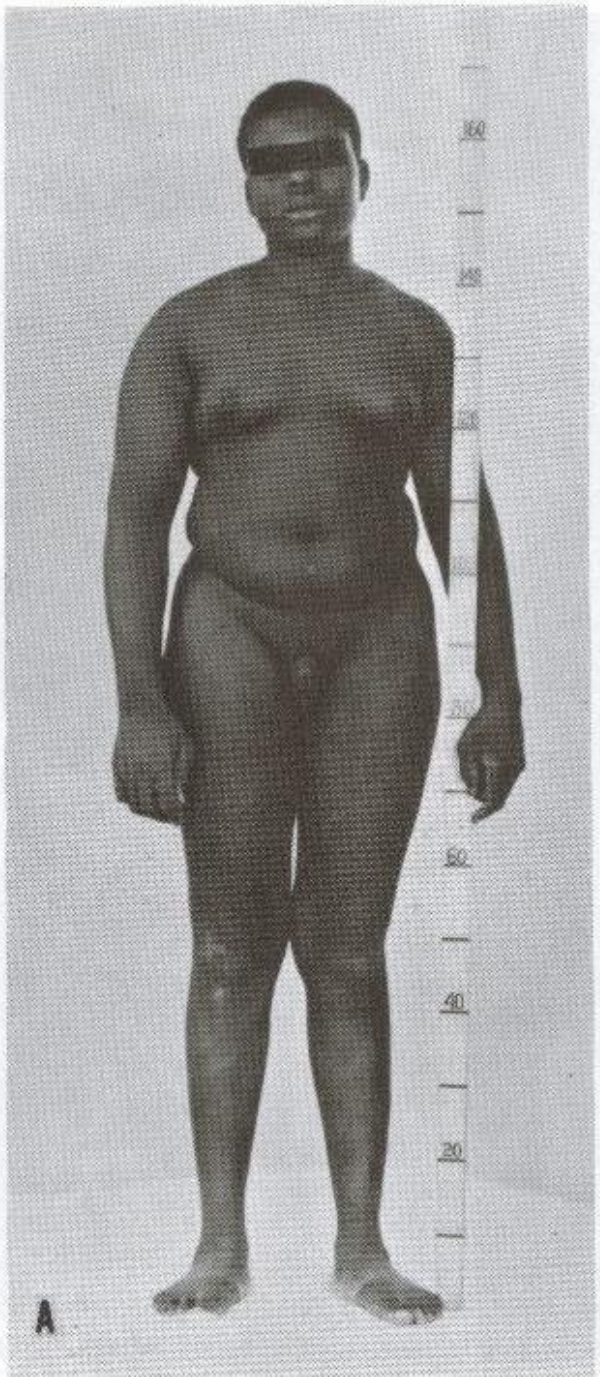
(= true hermaphrodism)

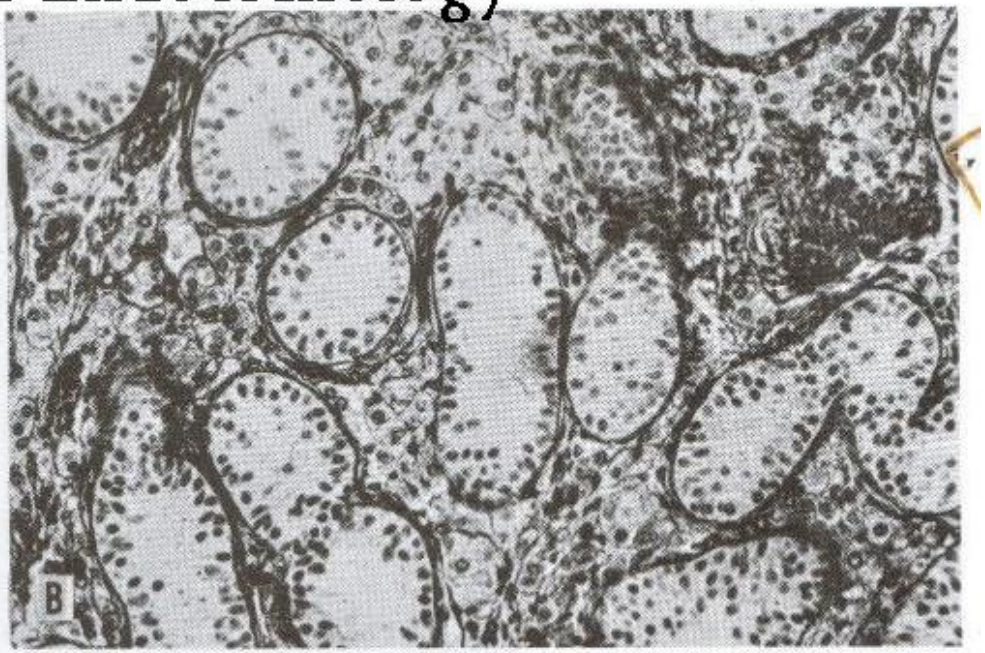
Presence of both ovarian and testicular tissues

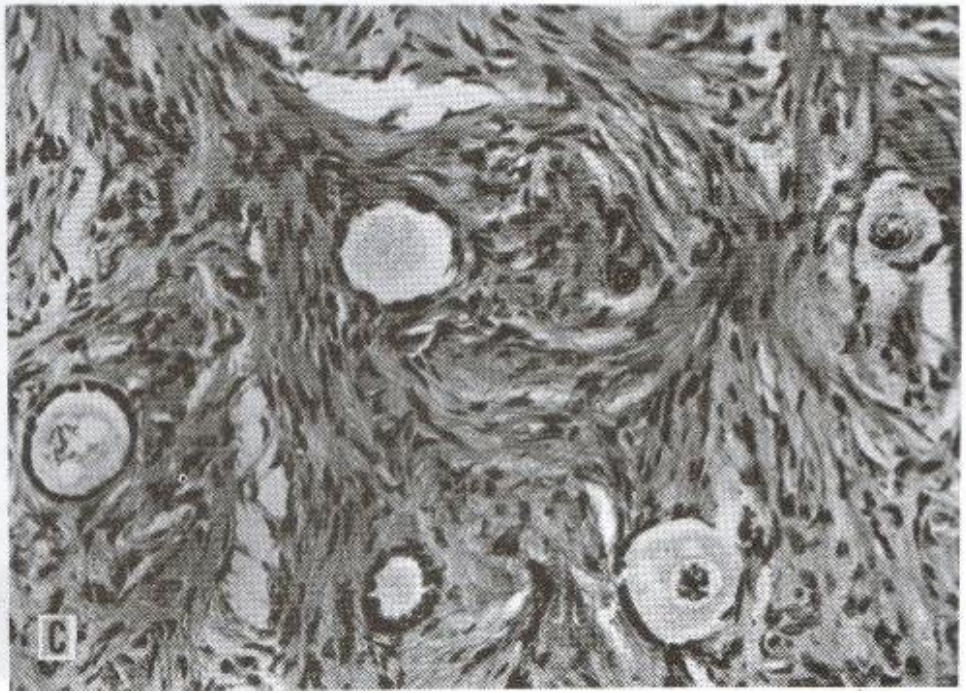
(1 ovary/1 testis, 2 ovotestes, 1 ovotestis/1ovary or 1 testis)

- 46,XX/46,XY chimerism (30%)
- *46,XX (60%)*
- *46, XY (10%)*

Williams Textbook of Endocrinology



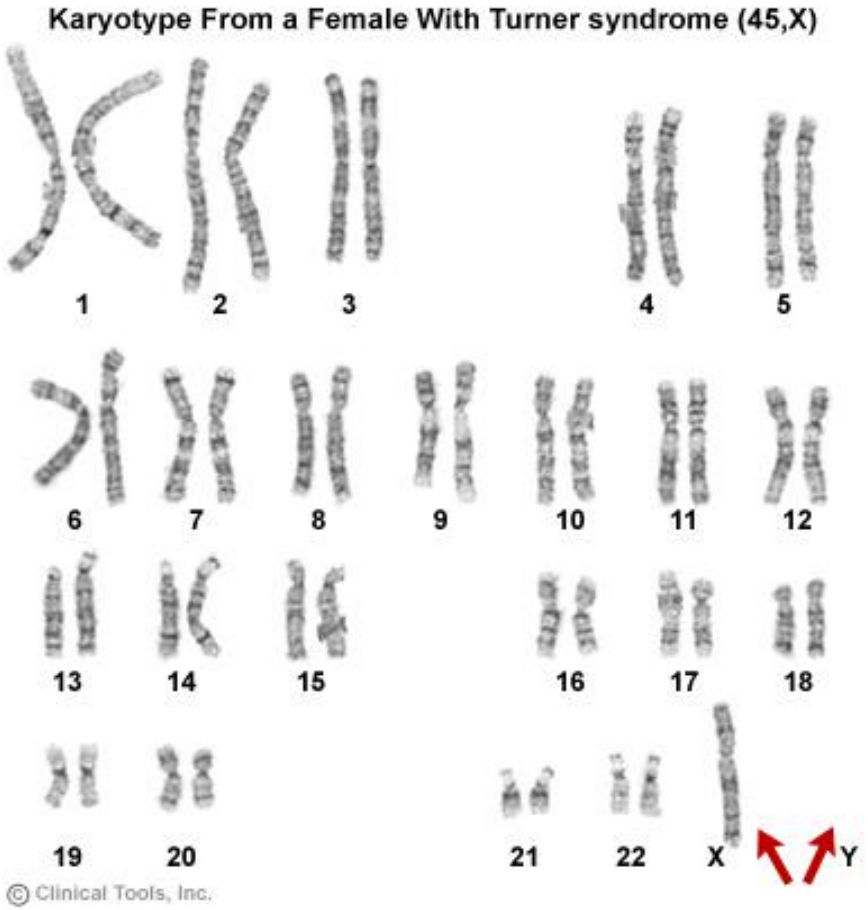





Primary follicles
Ovarian stroma
Sertoli cell
Spermatogonia

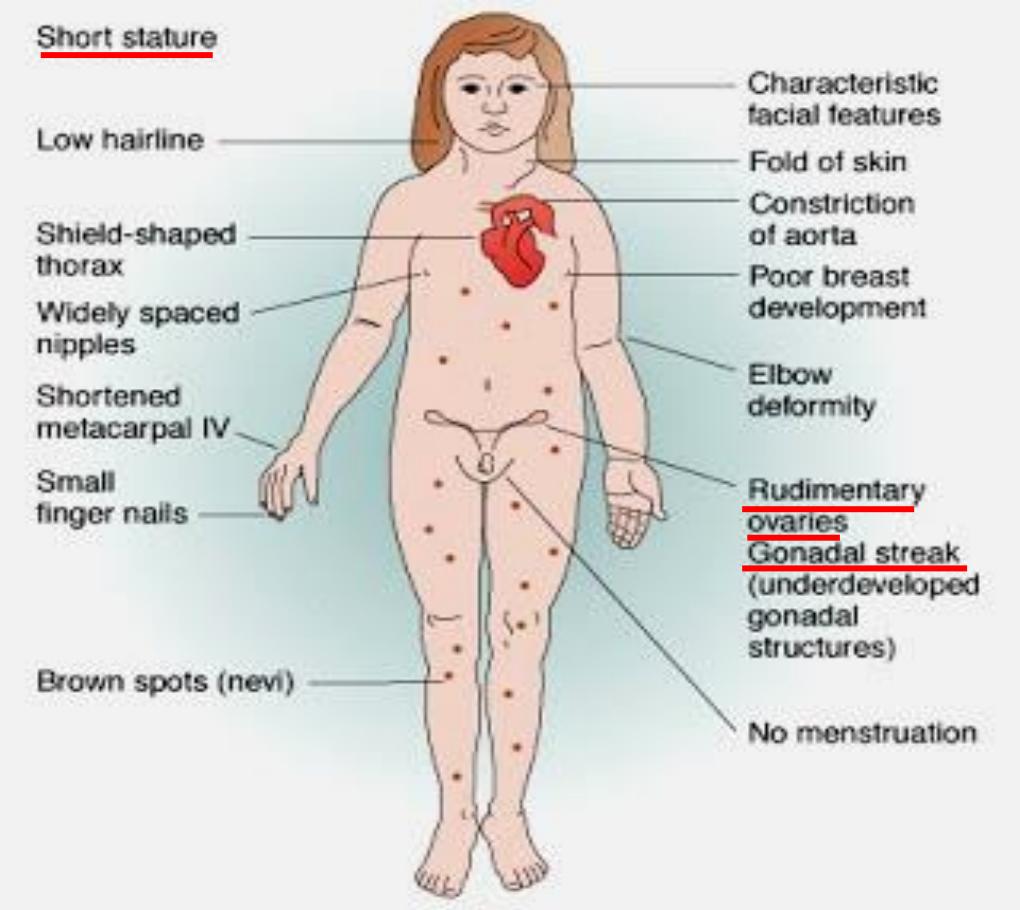
ovotestis

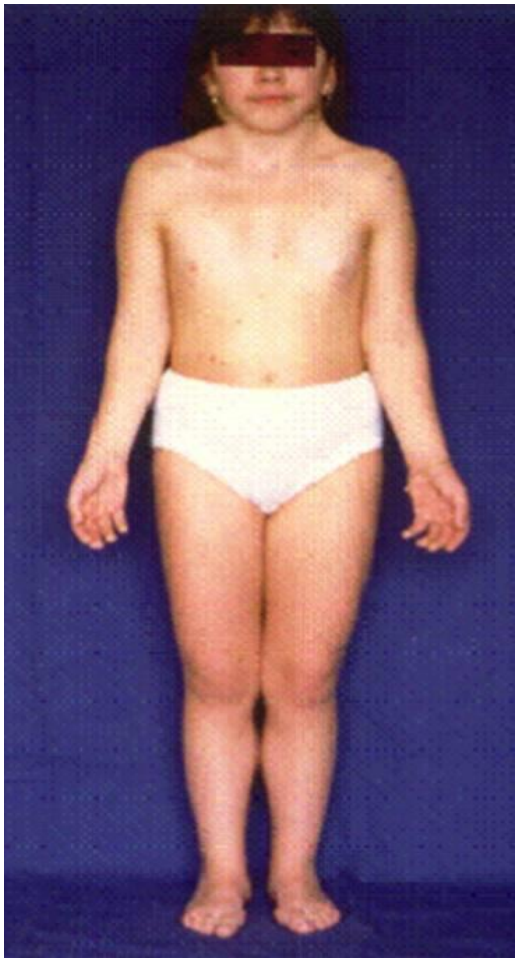
2. 45,X and Turner variants



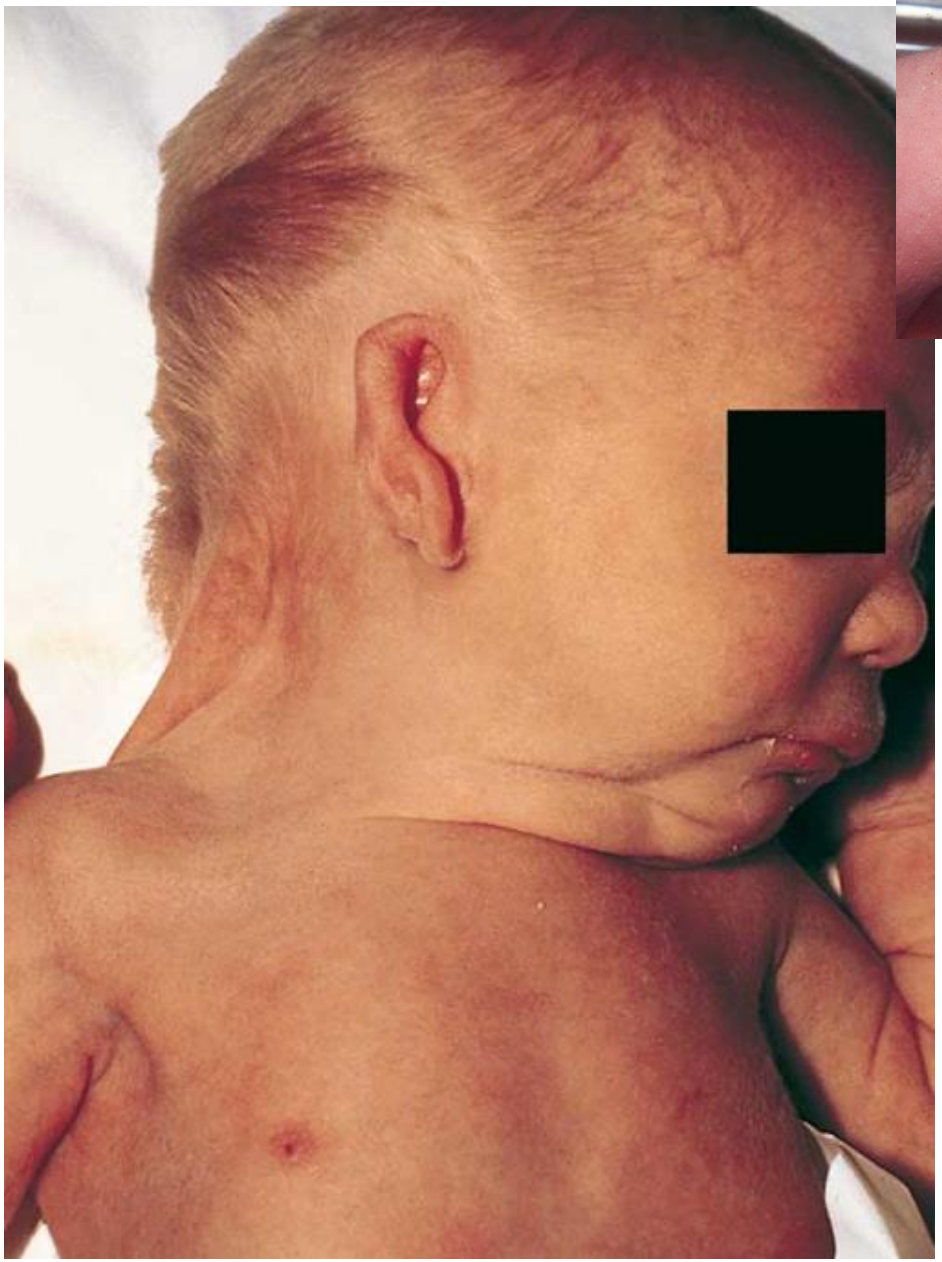
>99% : spontaneous abortion

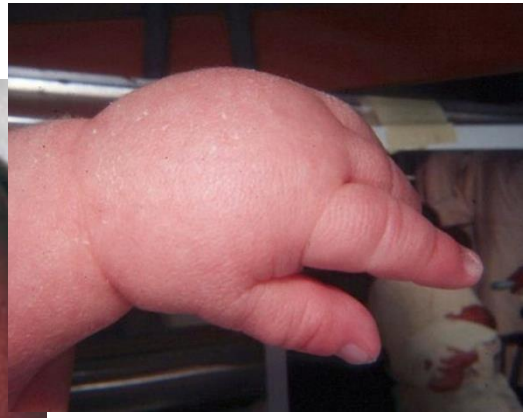
Incidence at birth: 1/4000 - 1/5000

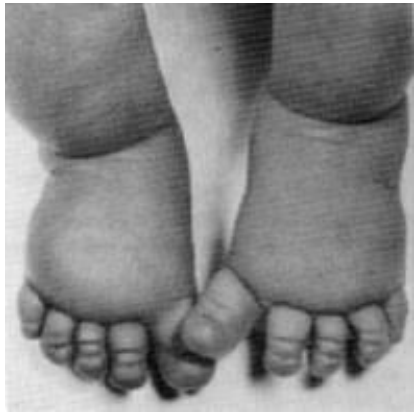




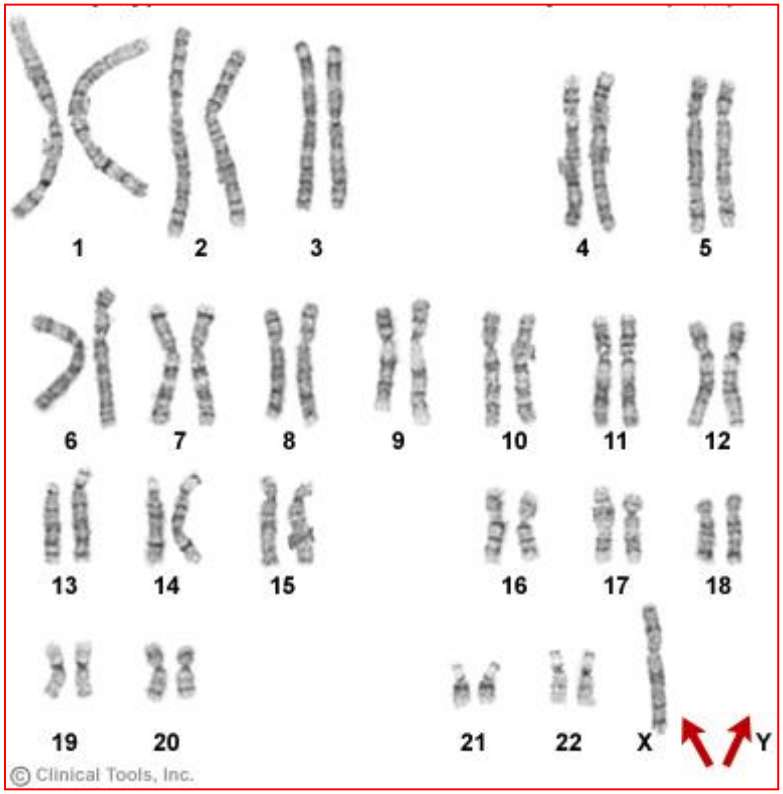
- **Delayed sexual maturation (R/ estrogene), amenorrhea, infertility**
- **Short stature (R/growth hormone)**
- **Pterygium colli, widely spaced nipples, cubitus valgus**
- **Cardiac malformation, hands and feet lymphedema**
- **Renal malformation**
- **No intellectual disability**







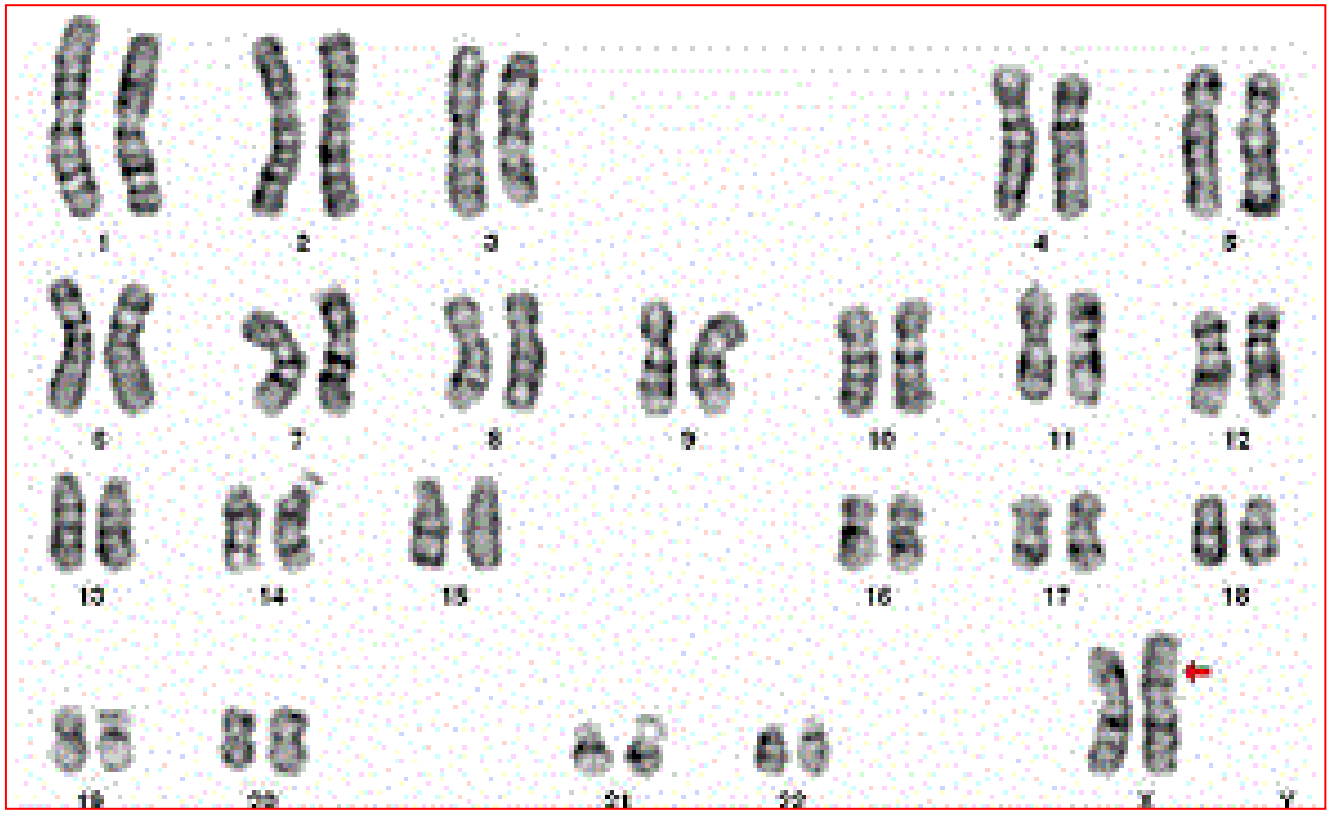
Turner Syndrome and variants

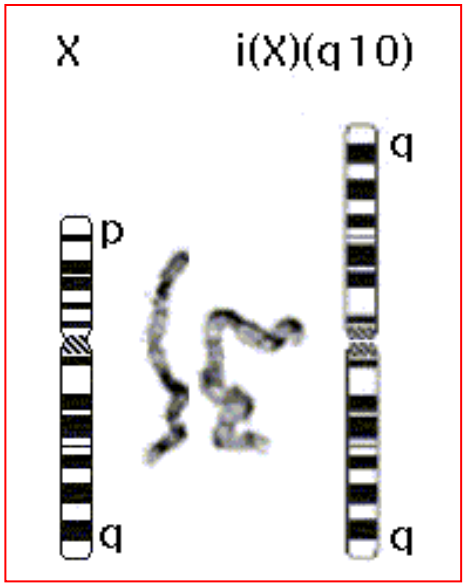


45, X

- 45, X : 50%
- 46, X, i(Xq): 15%
- 45,X/46,XX mosaic: 15%
- 45,X/46,X,i(Xq) mosaic: about 5%
- other X abnormalities (ringX,…): about 10%

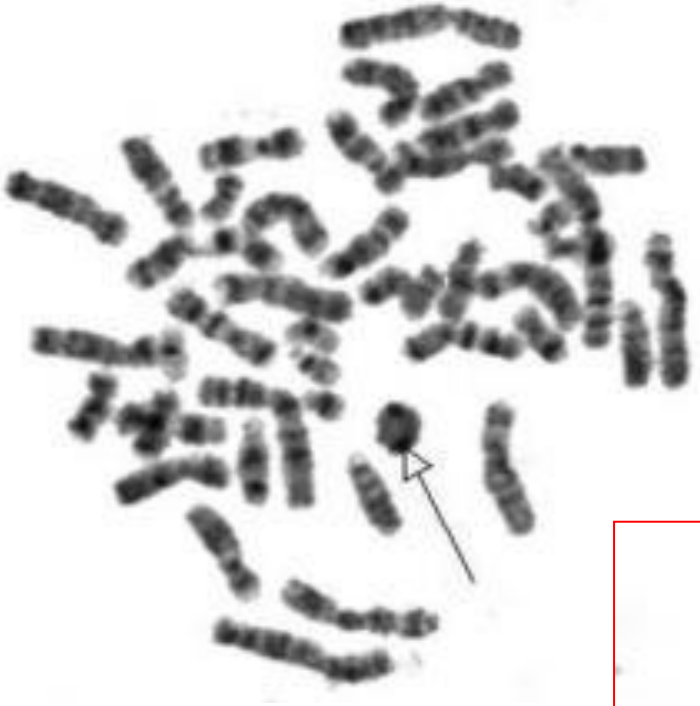
Turner Syndrome (variant)

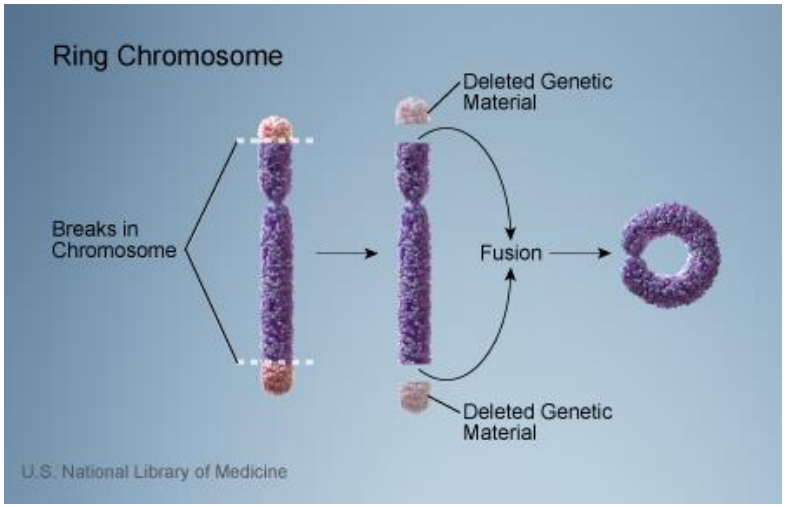


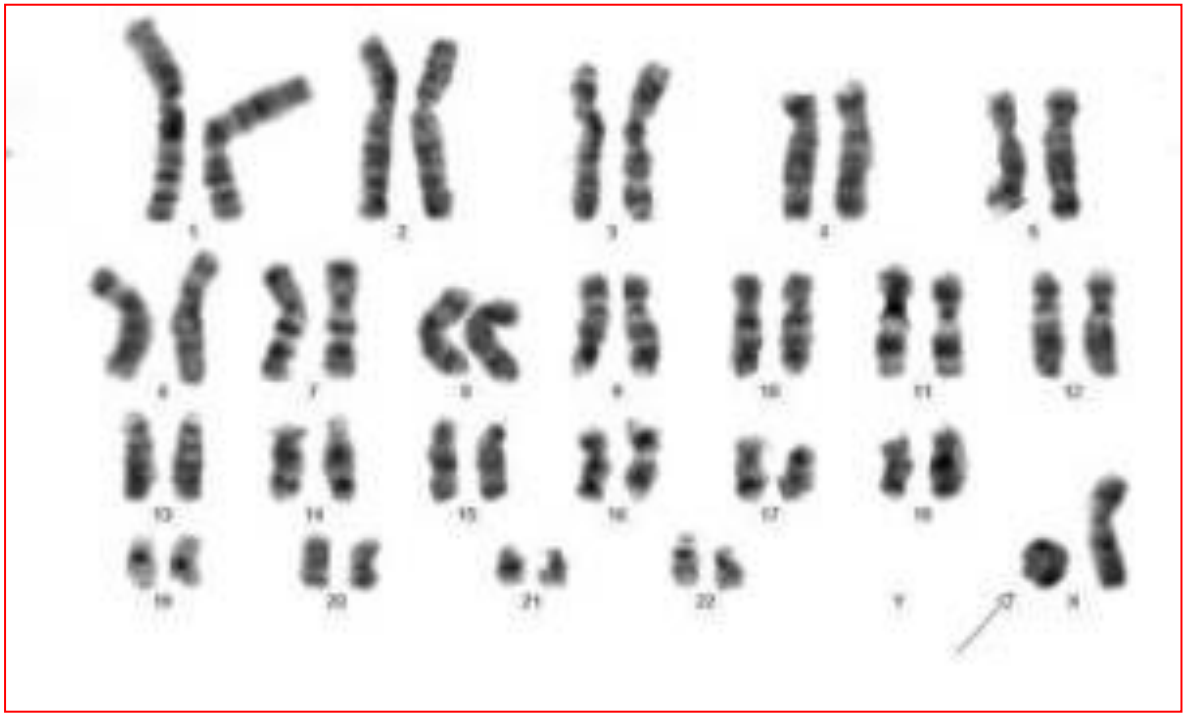


46, X, i(Xq)

Turner Syndrome (variant)

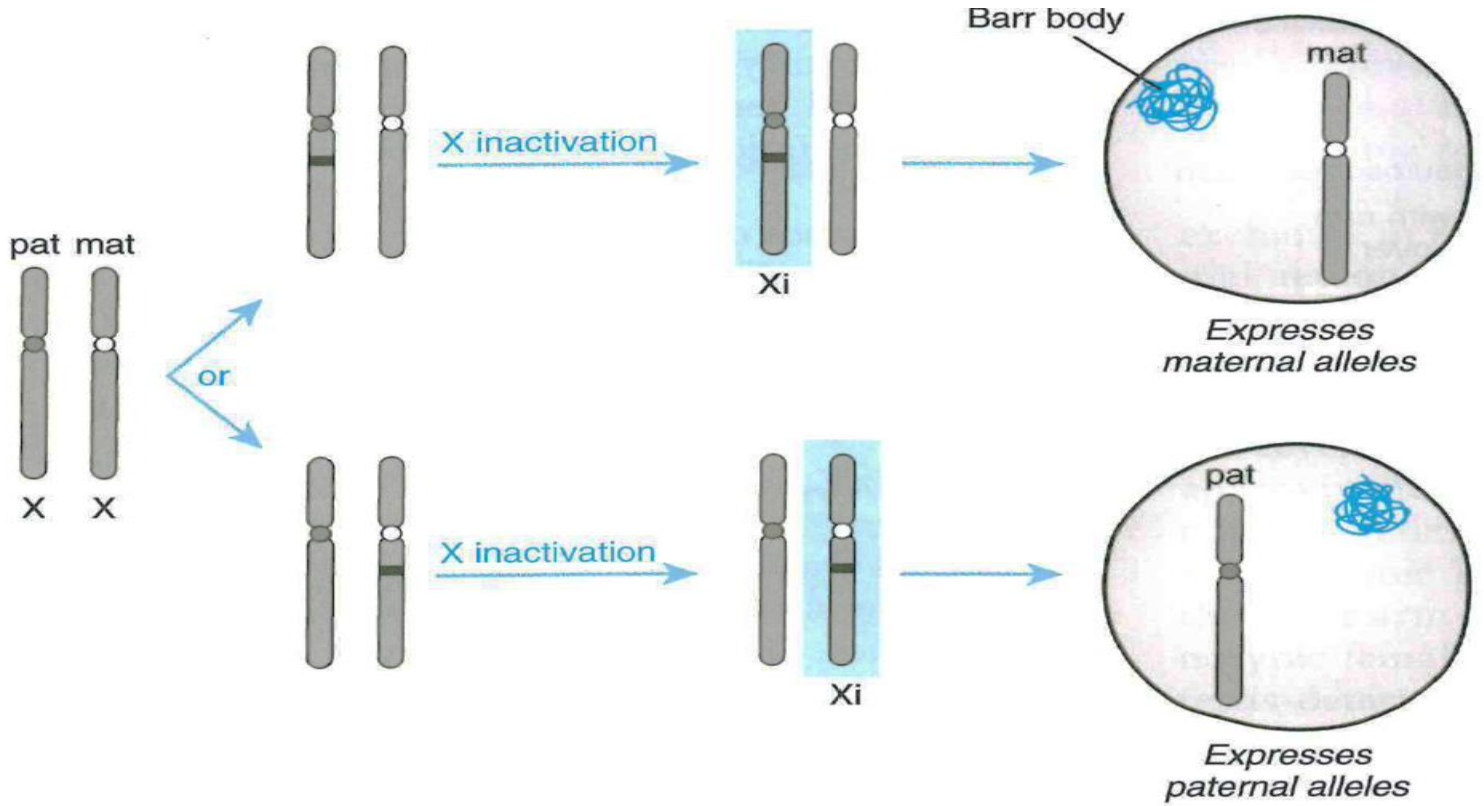






46, X, r(X)

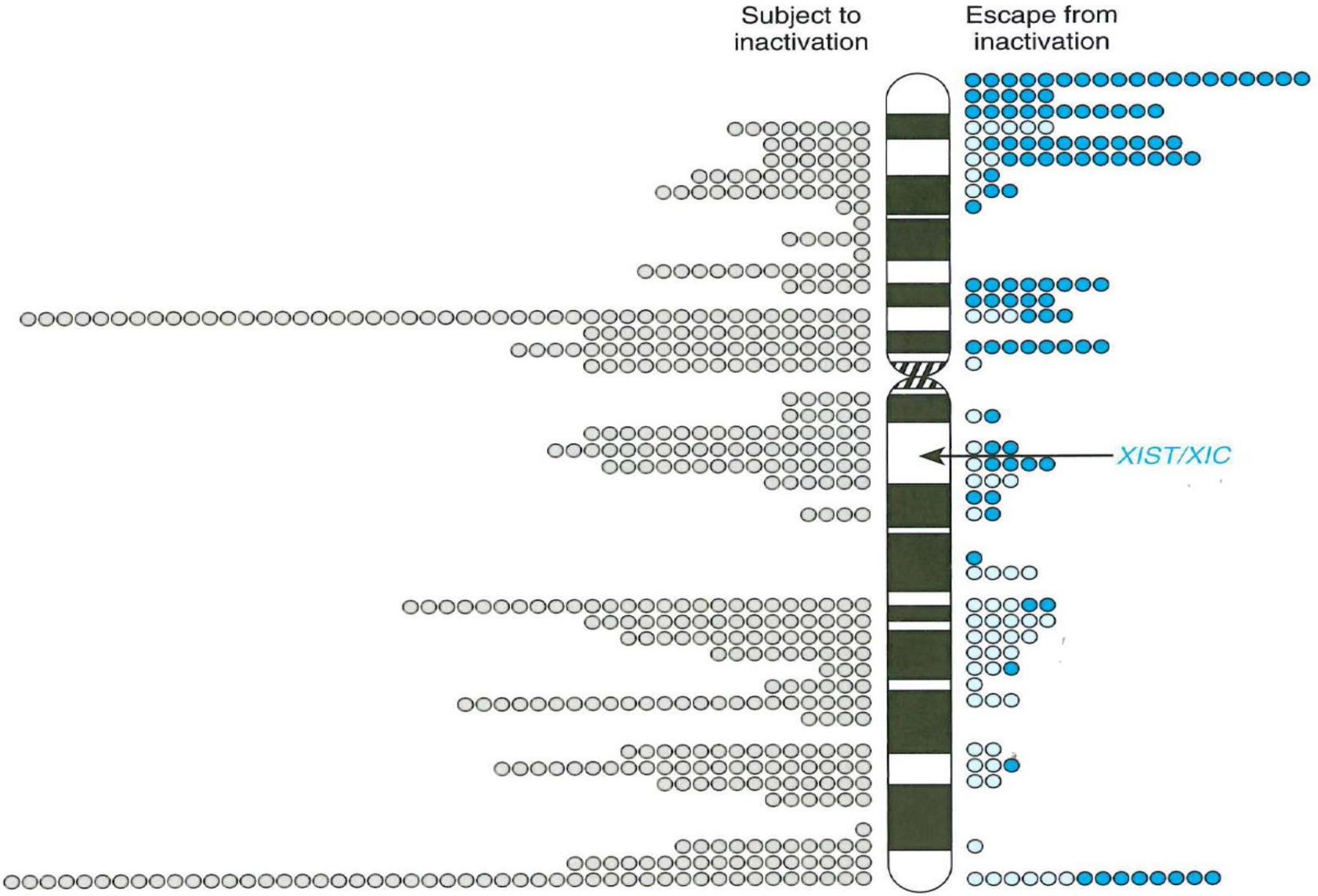
The X chromosome



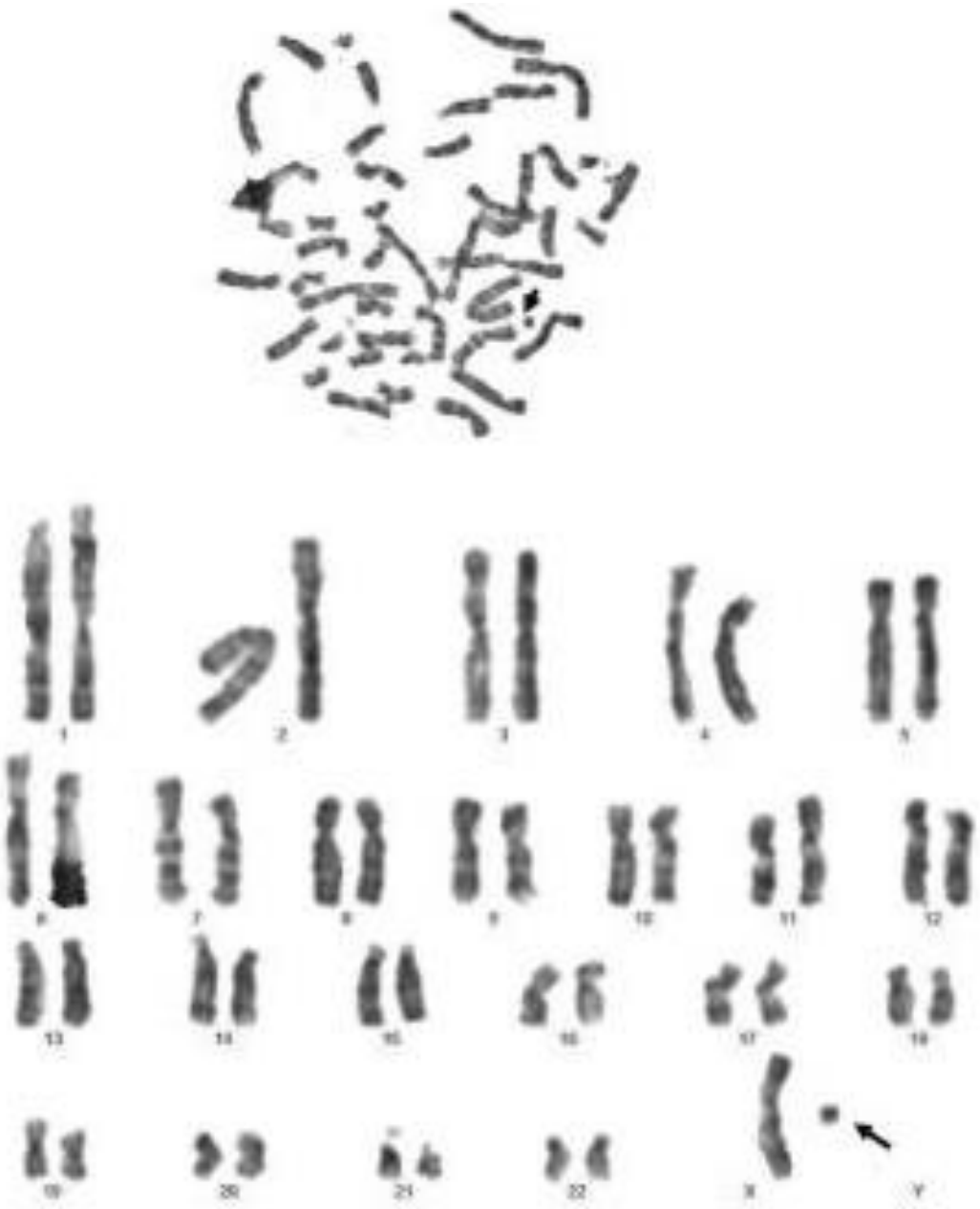
Random X chromosome inactivation early in female development by X inactivating center (XIST/XIC) in Xq13.2 (DNA méthylation, macroH2A histone modifications, …)

ⓘ Not Random if abnormal X chromosome (Skewed X-inactivation)

The X chromosome



At least 15% of genes escape to X inactivation and are expressed from both active and inactive X chromosomes



Particular case:

Small ring X chromosome

↓

Loss of the XIST locus
No X inactivation

↓

Genes overexpression

↓

Intellectual disability

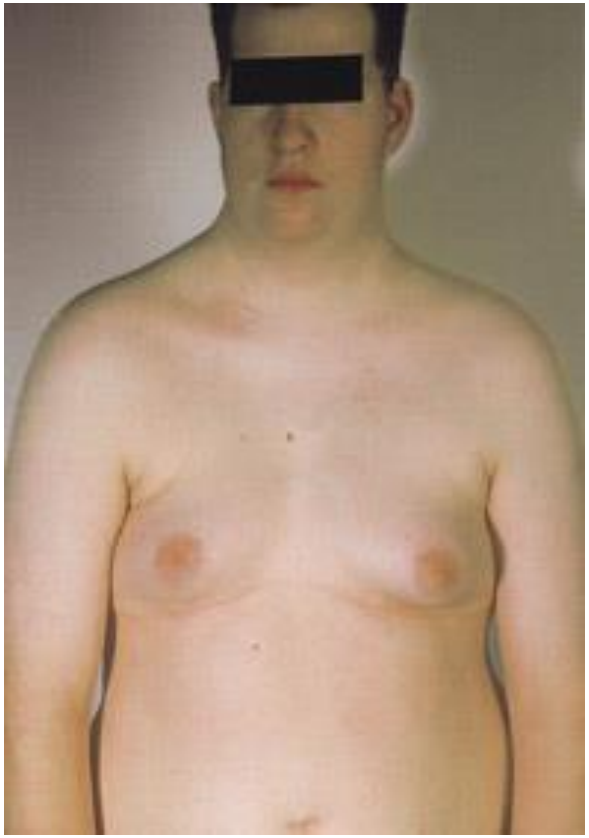
Rem: 47,XXX (trisomy X)

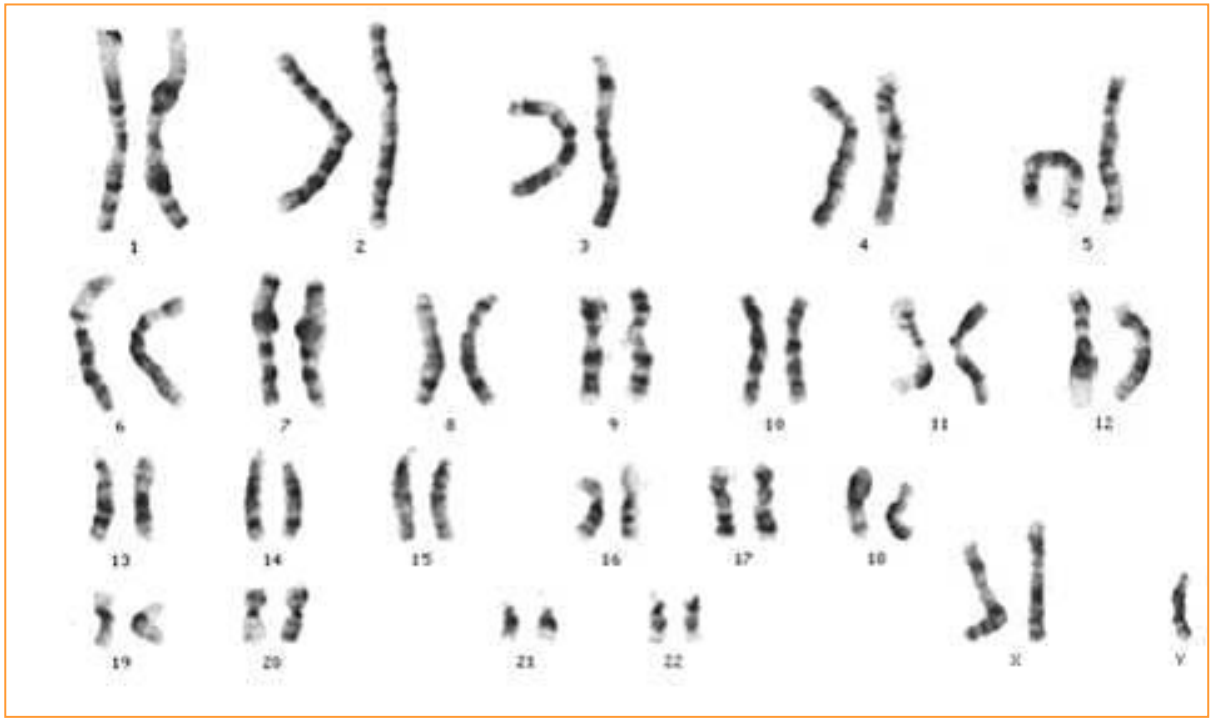
- Incidence 1/1000 female births
- Normal phenotype (above average stature)
- No infertility
- No intellectual disability but 70% learning problems
- Abnormal behavior?

Rem: 48,XXXX or 49, XXXXX

- More severe phenotype, intellectual disability

3. 47,XXY and Klinefelter variants

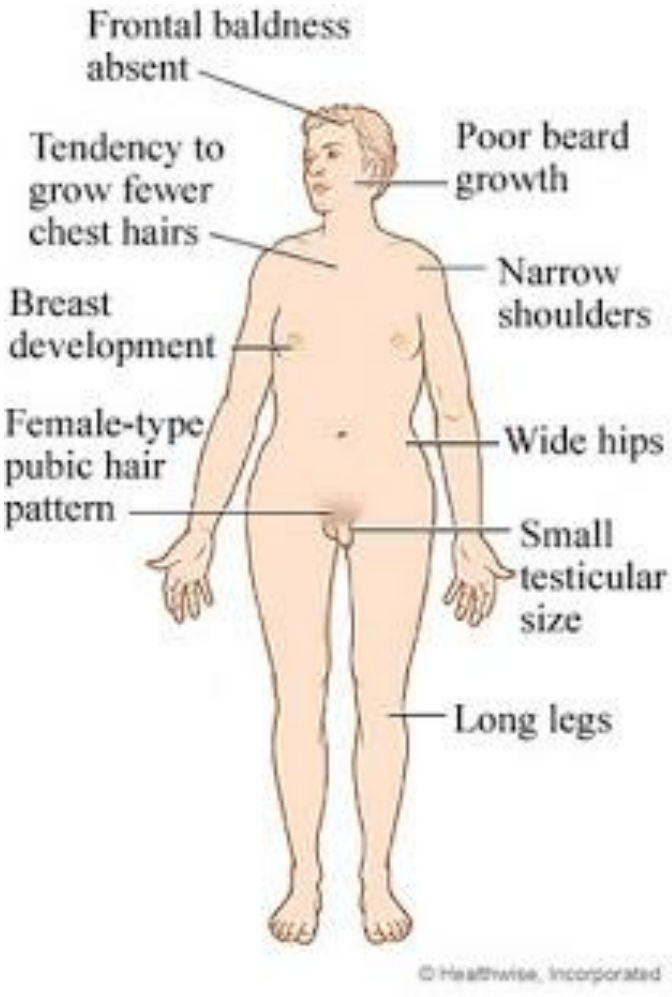


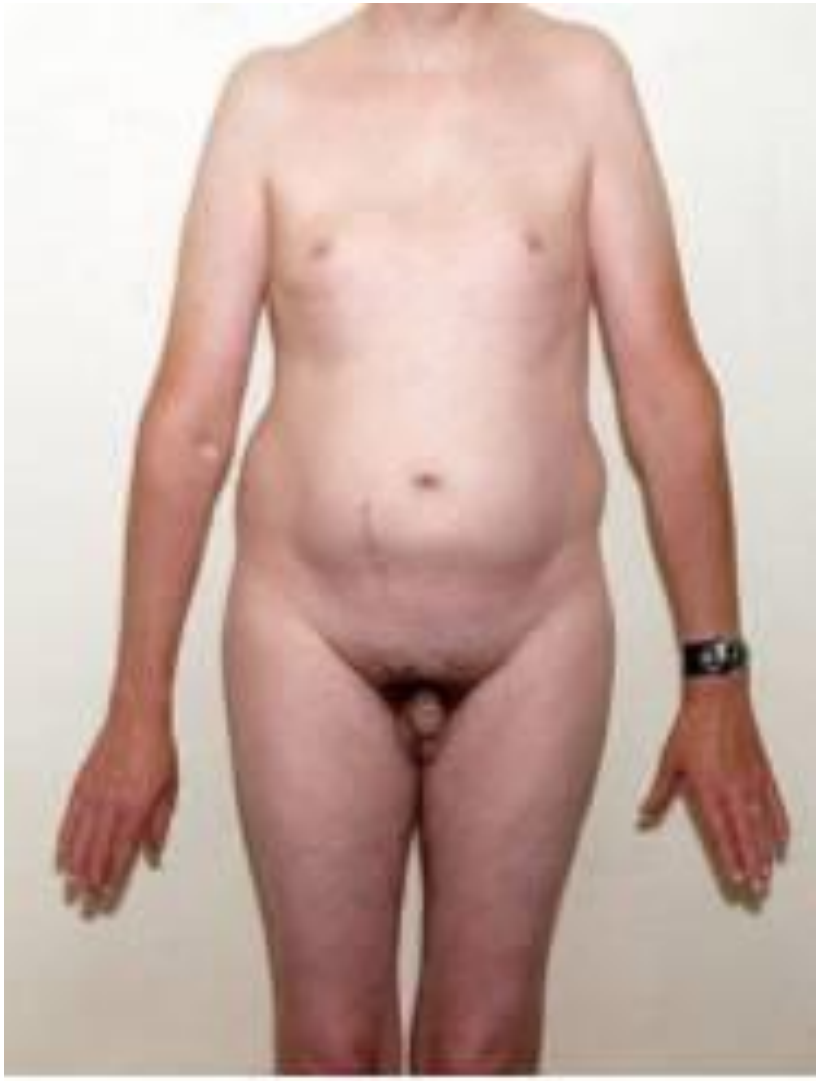


47, XXY

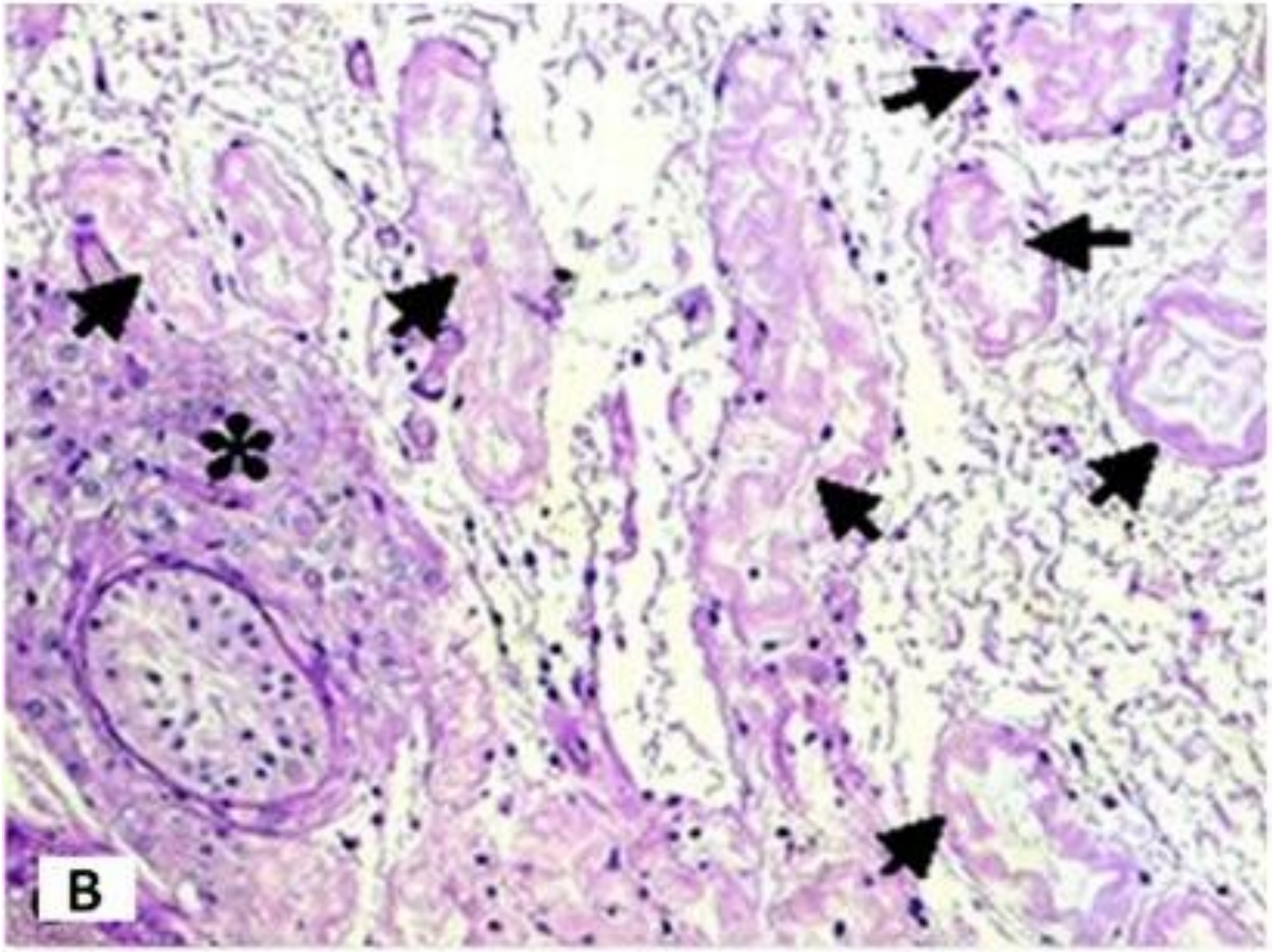
Maternal or paternal meiosis non disjunction

Incidence: 1/1000 male live births





- **Tall, long legs**
- **Narrow shoulders**
- **Gynecomastia (risk breast cancer X20 – X50)**
- **Hypogonadism, small genitalia, decreased muscle tone (R/androgenes)**
- **Infertility by seminiferous tubes hyalinosis (R/ ICSI)**
- **No intellectual disability (but sometimes learning difficulties and poor psychosocial adjustment)**



- Hyalinized seminiferous tubules (→)
- Nodules of Leidig cells (*)

Klinefelter Syndrome (variants)

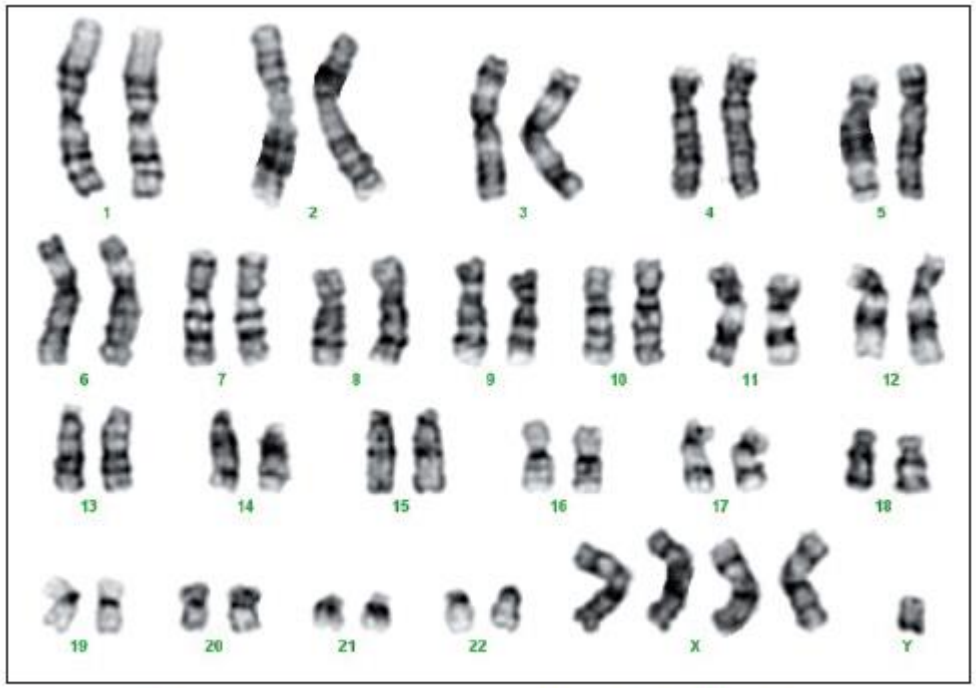


Figure 1: Karyogram showing the 49,XXXXY karyotype.

- 47, XXY : >80%
- Mosaic kayotype (46,XY/47,XXY): 15%
- 48,XXYY
- 48,XXXY
- 49,XXXXY

More severe phenotype (defective sexual development, dysmorphism, intellectual disability)

Rem: 47,XYY condition

- Incidence 1/1000 male births
- Normal phenotype (tall stature)
- No infertility
- No intellectal disability (50% language delay)
- Attention deficit? Hyperactivity? Impulsiveness?

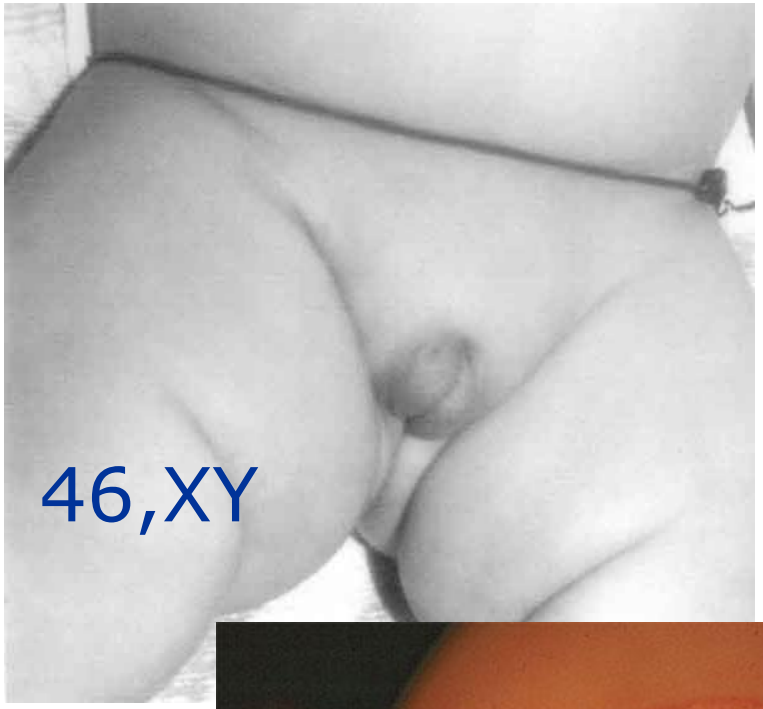
4. 45,X/46,XY mixed gonadal dysgenesis (MGD)

wide range of abnormalities:

- streak gonads, female phenotype and Turner syndrome
- ambiguous genitalia due to MGD (a streak gonad and a dysgenetic testis or two dysgenetic testes or undifferentiated gonadal tissue)
- ovotesticular DSD
- testes with almost normal histological features and normal male external genitalia

46,XY DSD
46,XX DSD

(Sex reversal and pseudohermaphroditism)



XX or XY?

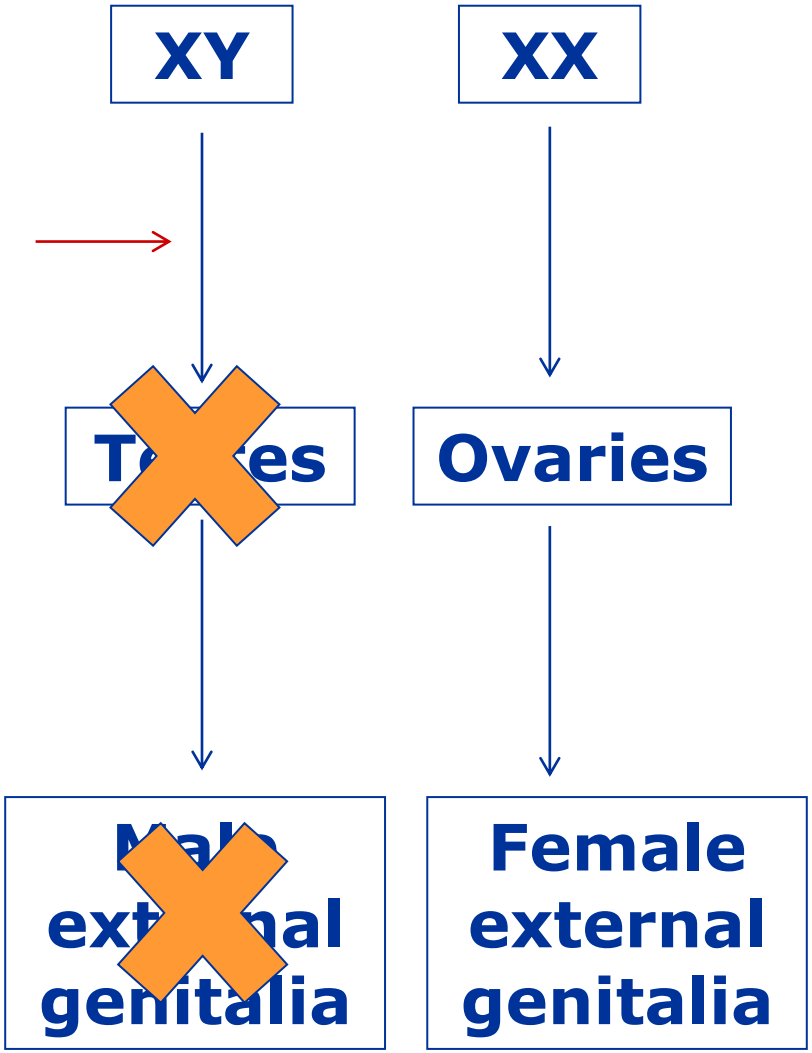
1. 46,XY DSD with gonadal dysgenesis

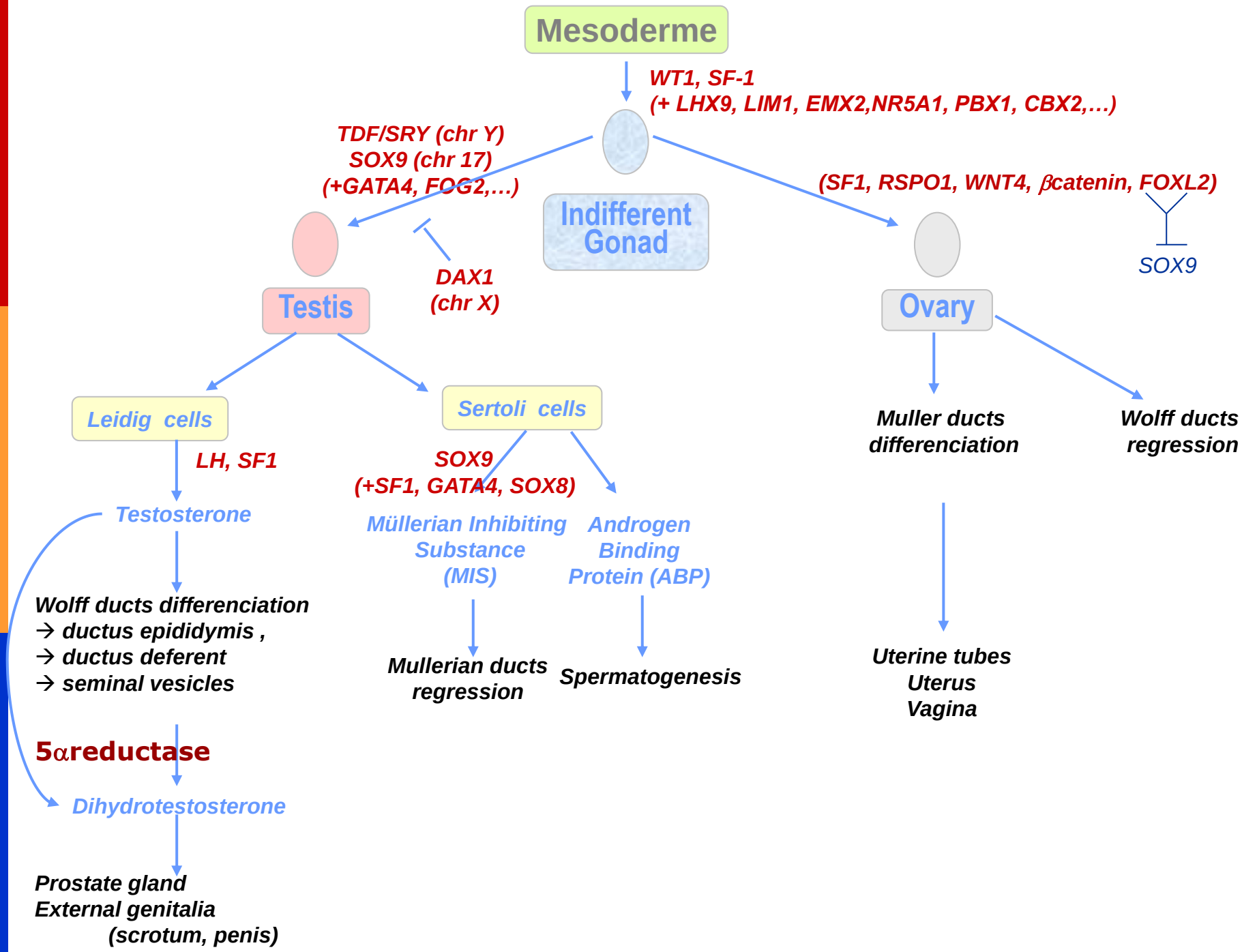
-46,XY

- gonadal dysgenesis
- female external genitalia (or ambiguous)

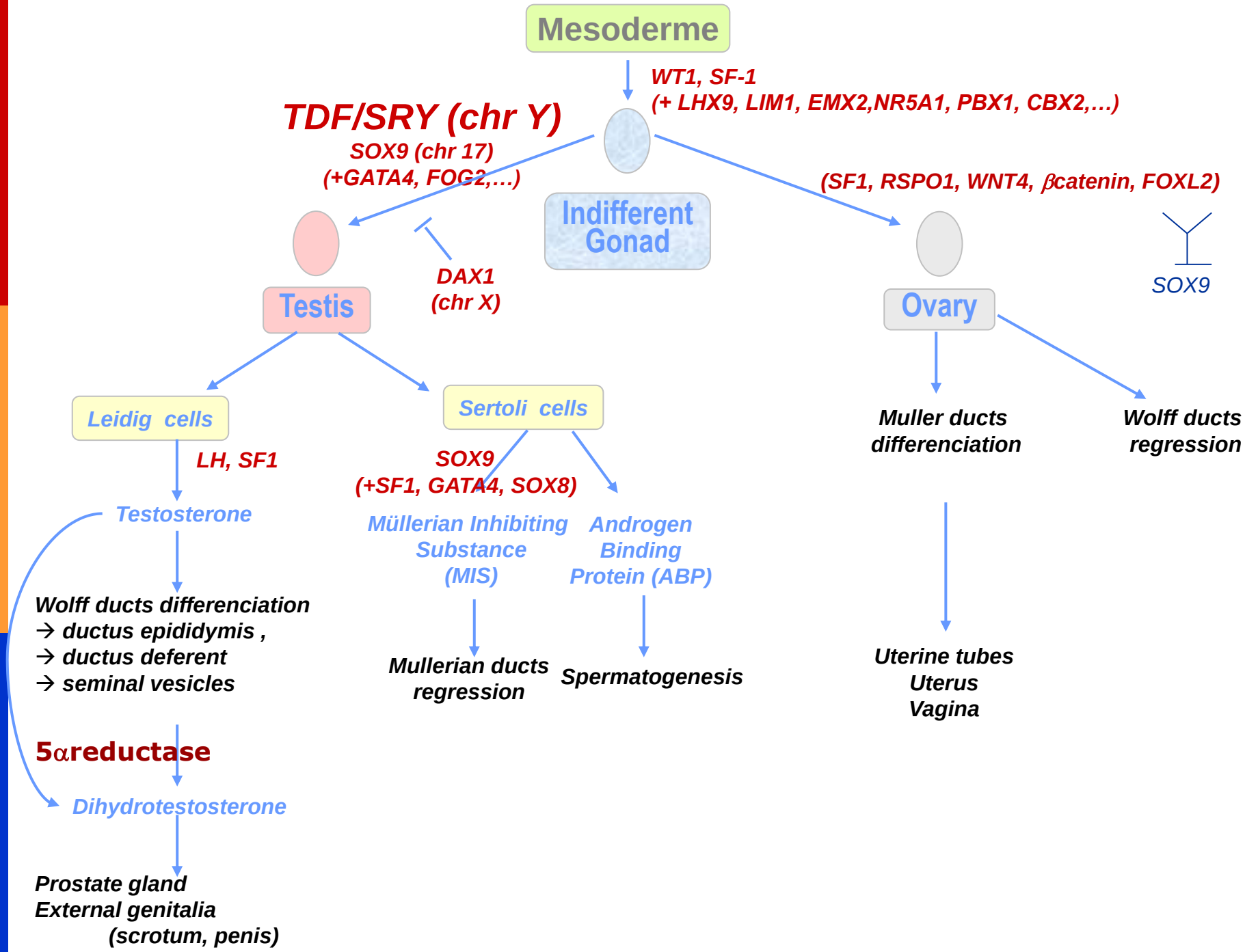
46,XY DSD

46,XY DSD with gonadal dysgenesis (« Female XY »)




Mesoderme
WT1, SF-1
(+ LHX9, LIM1, EMX2,NR5A1, PBX1, CBX2,…)
TDF/SRY (chr Y)
SOX9 (chr 17)
(+GATA4, FOG2,…)
(SF1, RSPO1, WNT4, βcatenin, FOXL2)
Indifferent Gonad
SOX9
DAX1
(chr X)
Testis
Ovary
Leidig cells
Sertoli cells
Muller ducts differenciation
Wolff ducts regression
LH, SF1
SOX9
(+SF1, GATA4, SOX8)
Testosterone
Müllerian Inhibiting Substance (MIS)
Androgen Binding Protein (ABP)
Wolff ducts differenciation
→ ductus epididymis ,
→ ductus deferent
→ seminal vesicles
Mullerian ducts regression
Spermatogenesis
Uterine tubes
Uterus
Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

- SRY Deletion or Mutation (Swyer)
- SOX9 Mutation
- SF1 mutation
- WT1 mutation
- DAX1 Duplication
- WNT4 Duplication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Vagina
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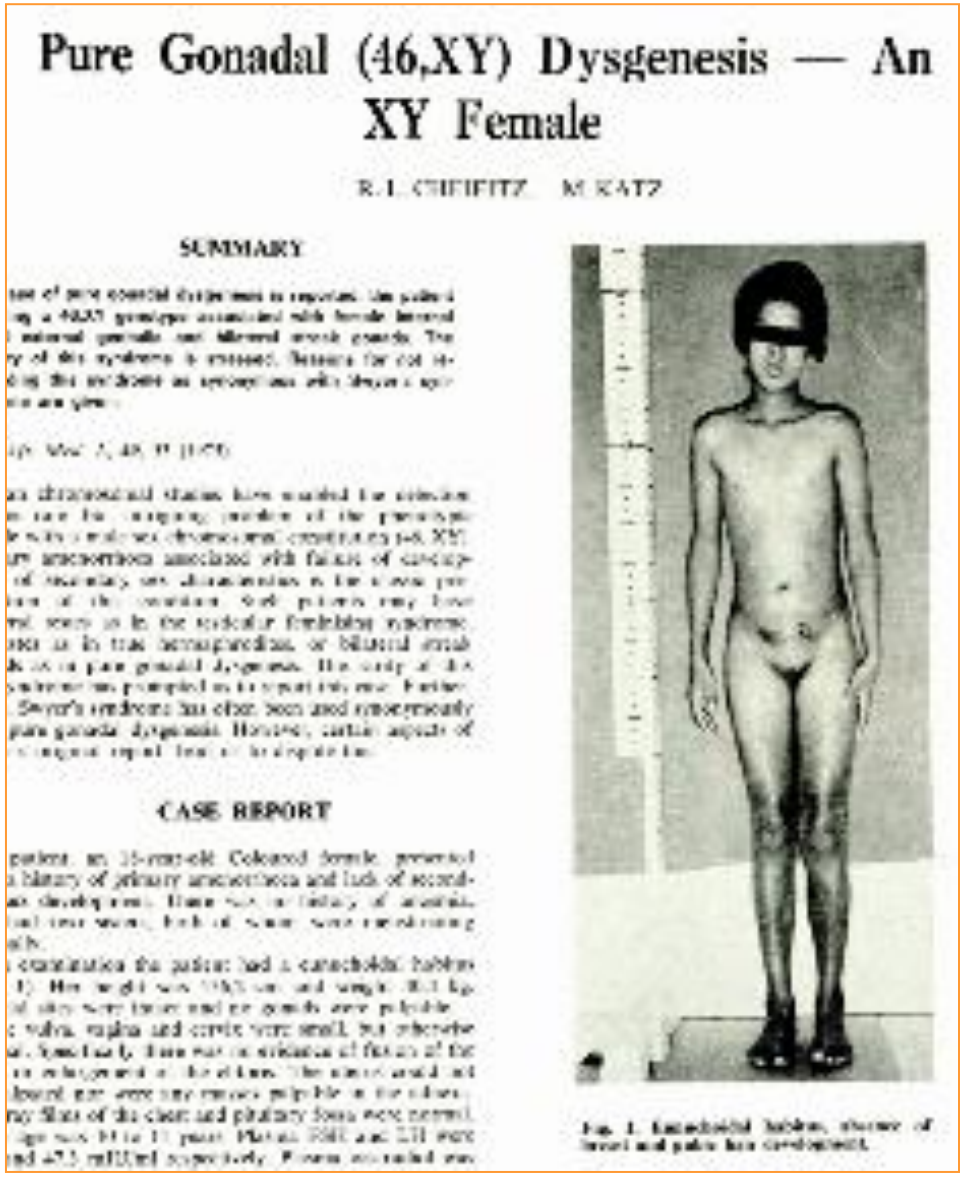
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

46,XY and SRY deletion or mutation



Pure Gonadal (46,XY) Dysgenesis — An XY Female

R.L. CHEIFITZ M. KATZ

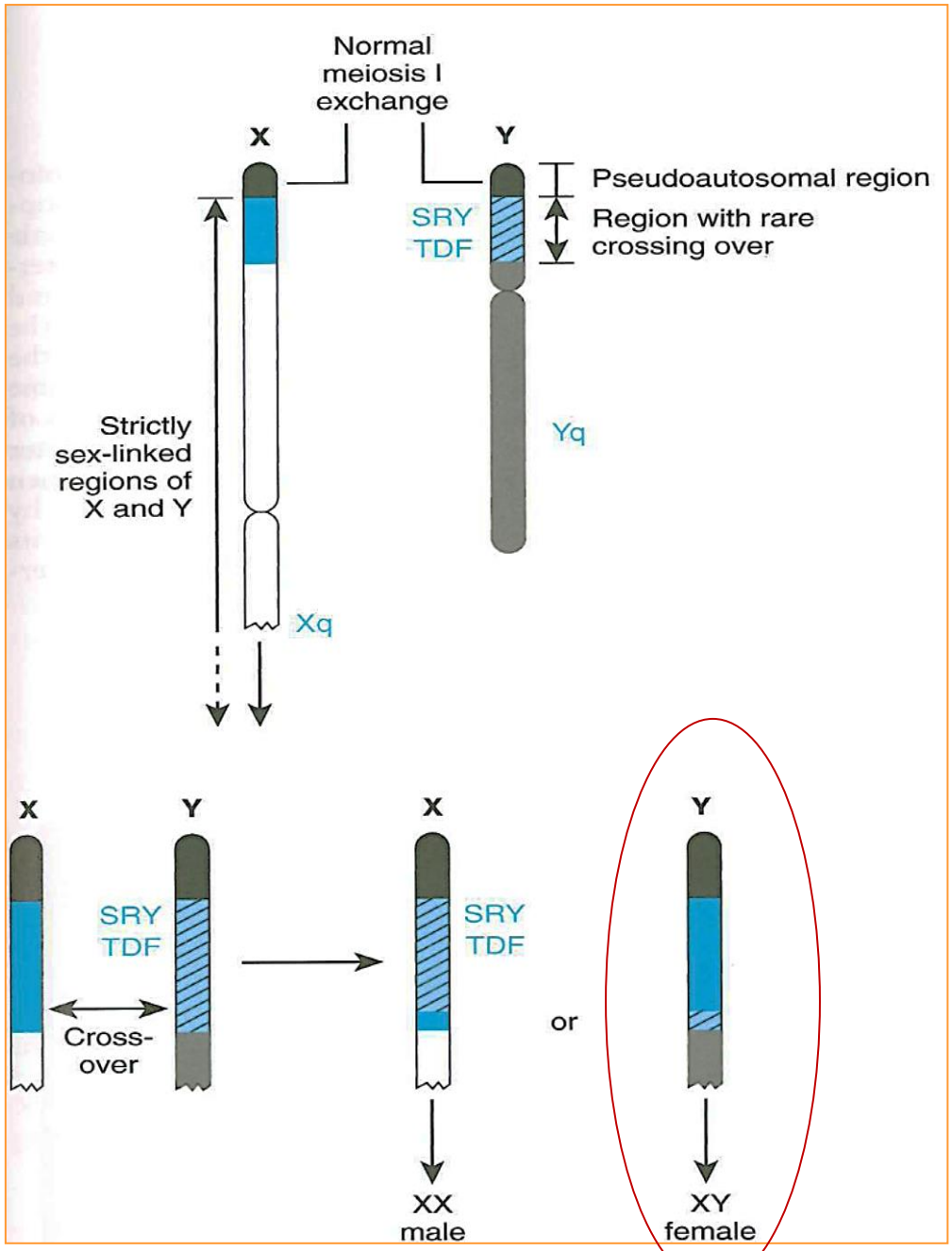
SUMMARY

CASE REPORT

- 46,XY
- gonadal dysgenesis
- Female external phenotype

(but amenorrhea and no secondary sexual characters)

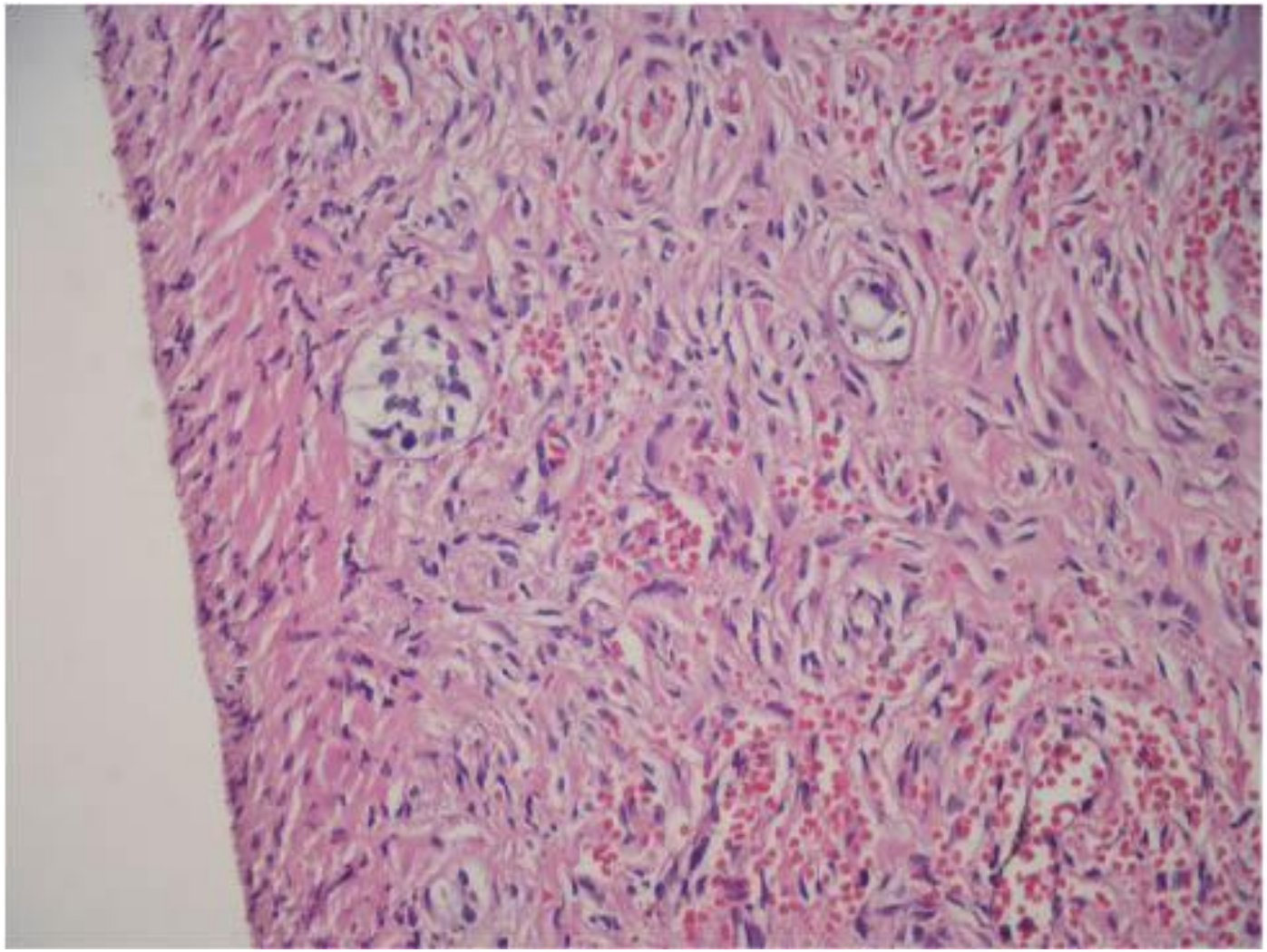
= SWYER syndrome



SRY = TDF
(testis-determining factor)

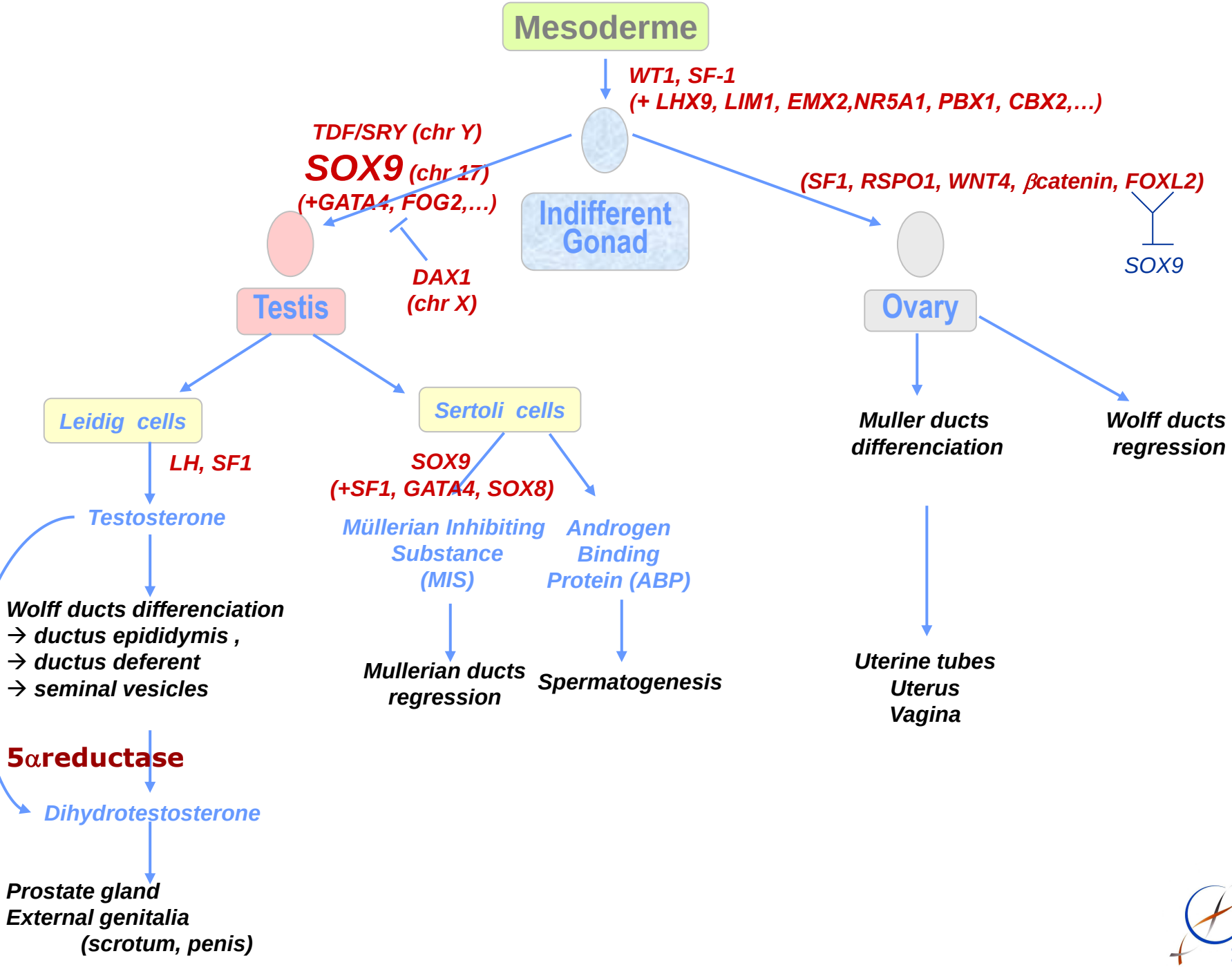
If genetic recombination outside the pseudoautosomic region (incidence 1/20000):

- XX male (with the SRY gene on a X chromosome)
- **XY female (without the SRY gene on the Y chromosome)**



Swyer syndrome: complete gonadal dysgenesis

IPG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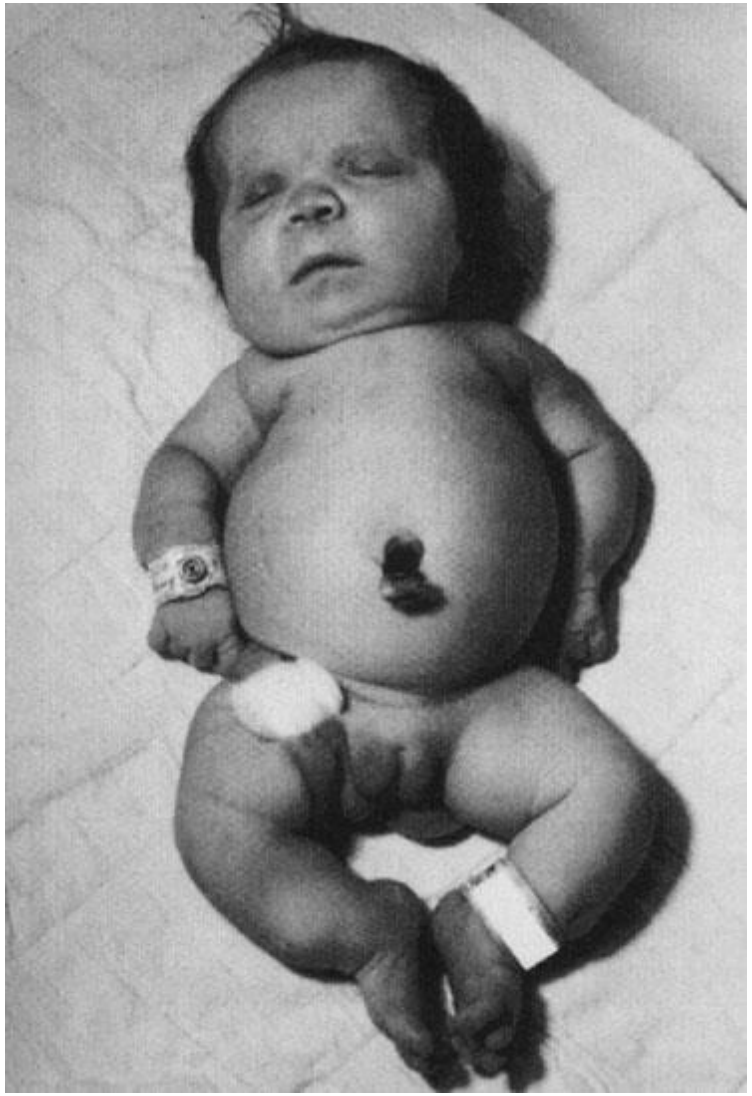
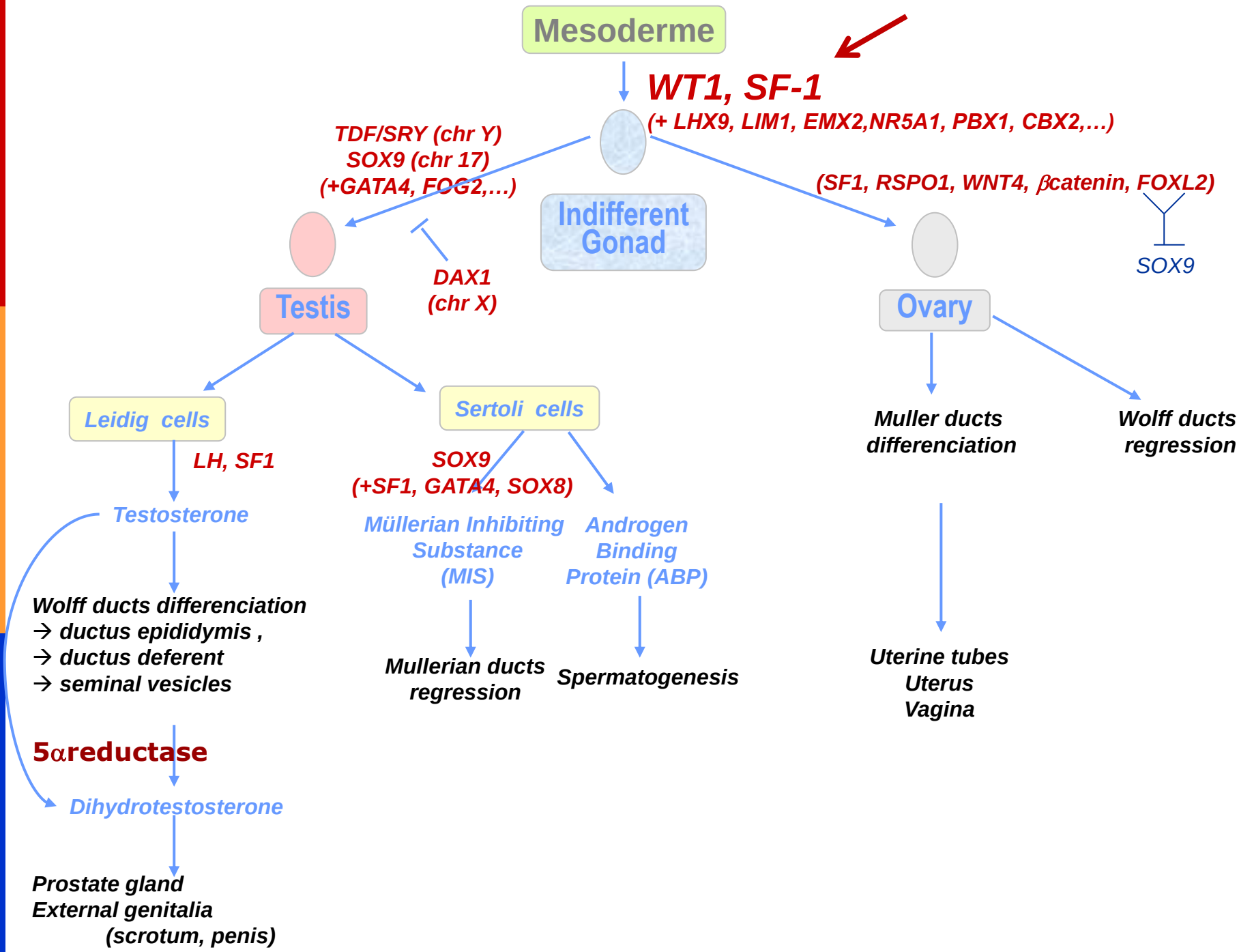
Spermatogenesis
Uterine tubes
Uterus
Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

46,XY and SOX9 mutation

Female XY with campomelic dysplasia



- 46,XY
- Gonadal dysgenesis
- Female external phenotype
- Campomelic dysplasia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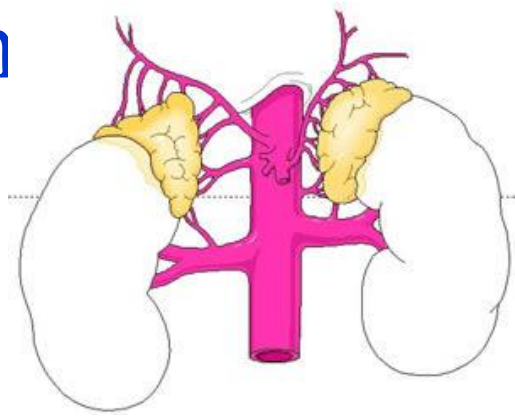
Uterus
Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

SF1 (NR5A1) gene mutation



46,XY and SF1 mutation:

- gonadal dysgenesis
- female or ambiguous external genitalia
- inconstant uterus
- adrenal insufficiency

Rem : 46,XX and SF1 mutation :

- Ovarian insufficiency

  (primary amenorrhea or premature ovarian failure)
- female external genitalia, uterus
- adrenal insufficiency

WT1 gene mutation

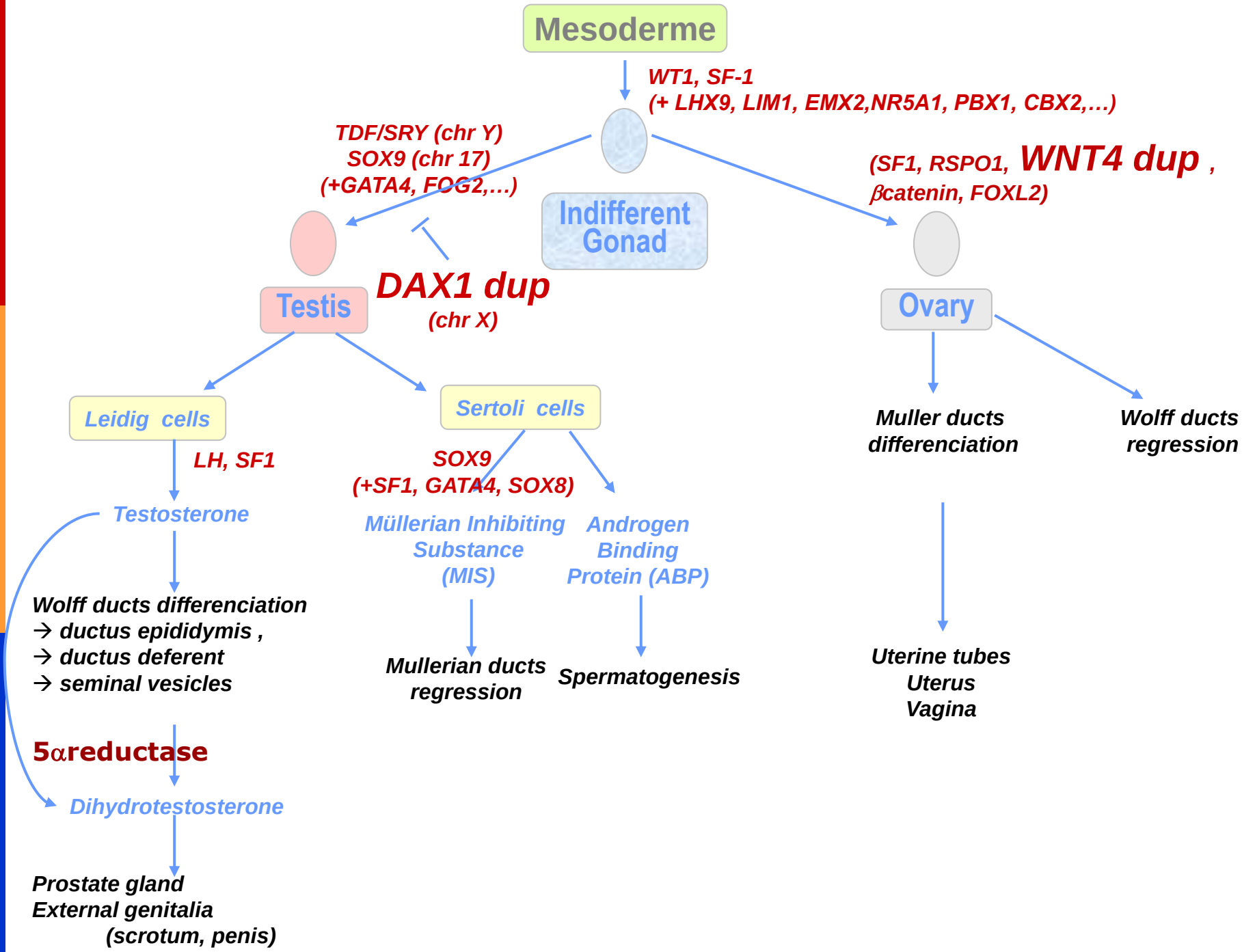
46,XY and WT1 mutation:

- gonadal dysgenesis
- female or ambiguous external genitalia
- inconstant uterus
- risk of Wilms tumor, nephropathy, aniridia

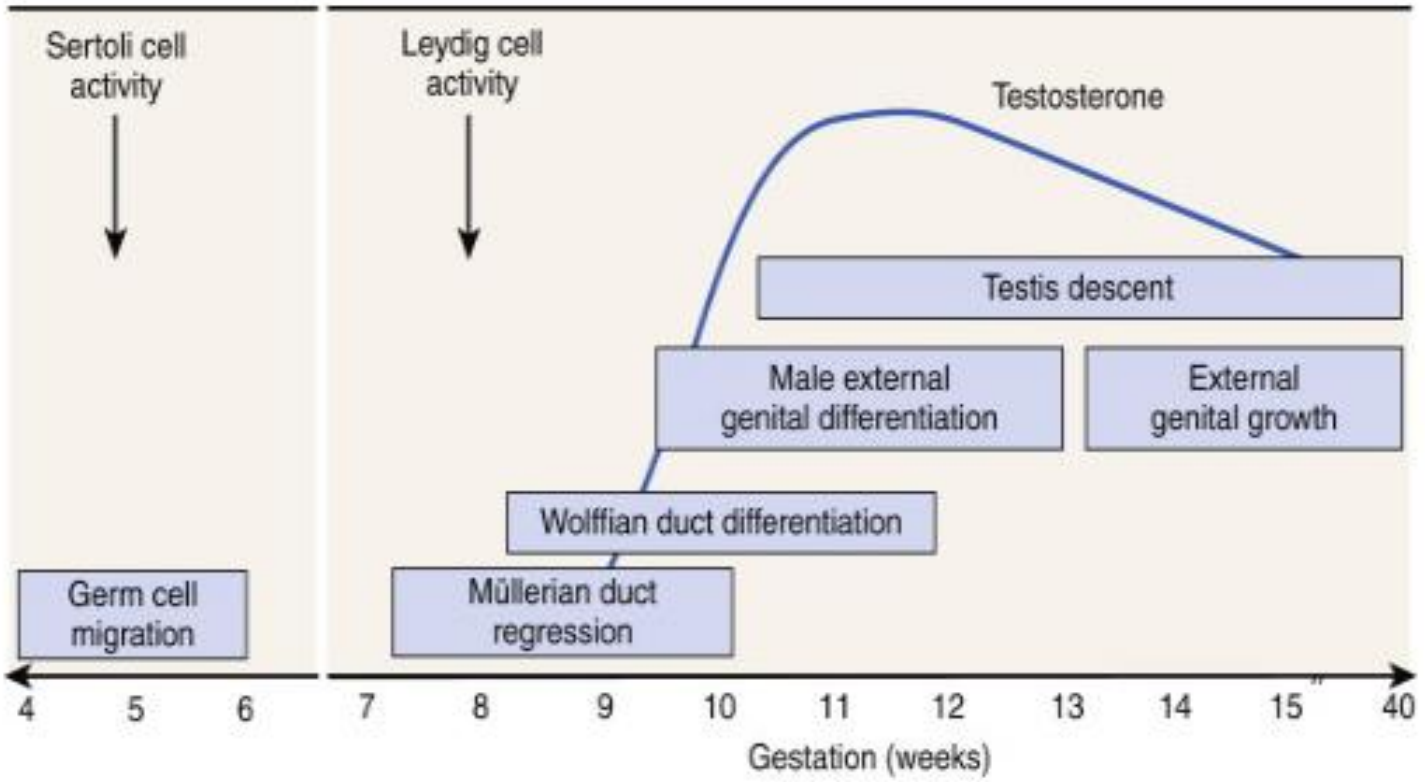
(Denys-Drash, Frasier and WAGR syndromes)

Rem: 46,XX and WT1 mutation :

-risk of Wilms tumor, nephropathy


Mesoderme
WT1, SF-1
(+ LHX9, LIM1, EMX2,NR5A1, PBX1, CBX2,…)
TDF/SRY (chr Y)
SOX9 (chr 17)
(+GATA4, FOG2,…)
(SF1, RSPO1, WNT4 dup , βcatenin, FOXL2)
Indifferent Gonad
DAX1 dup
(chr X)
Testis
Ovary
Leidig cells
Sertoli cells
LH, SF1
SOX9
(+SF1, GATA4, SOX8)
Testosterone
Müllerian Inhibiting Substance (MIS)
Androgen Binding Protein (ABP)
Muller ducts differenciation
Wolff ducts regression
Wolff ducts differenciation
→ ductus epididymis ,
→ ductus deferent
→ seminal vesicles
Mullerian ducts regression
Spermatogenesis
Uterine tubes
Uterus
Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

Rem: XY gonadal agenesis
= embryonic testicular regression syndrome



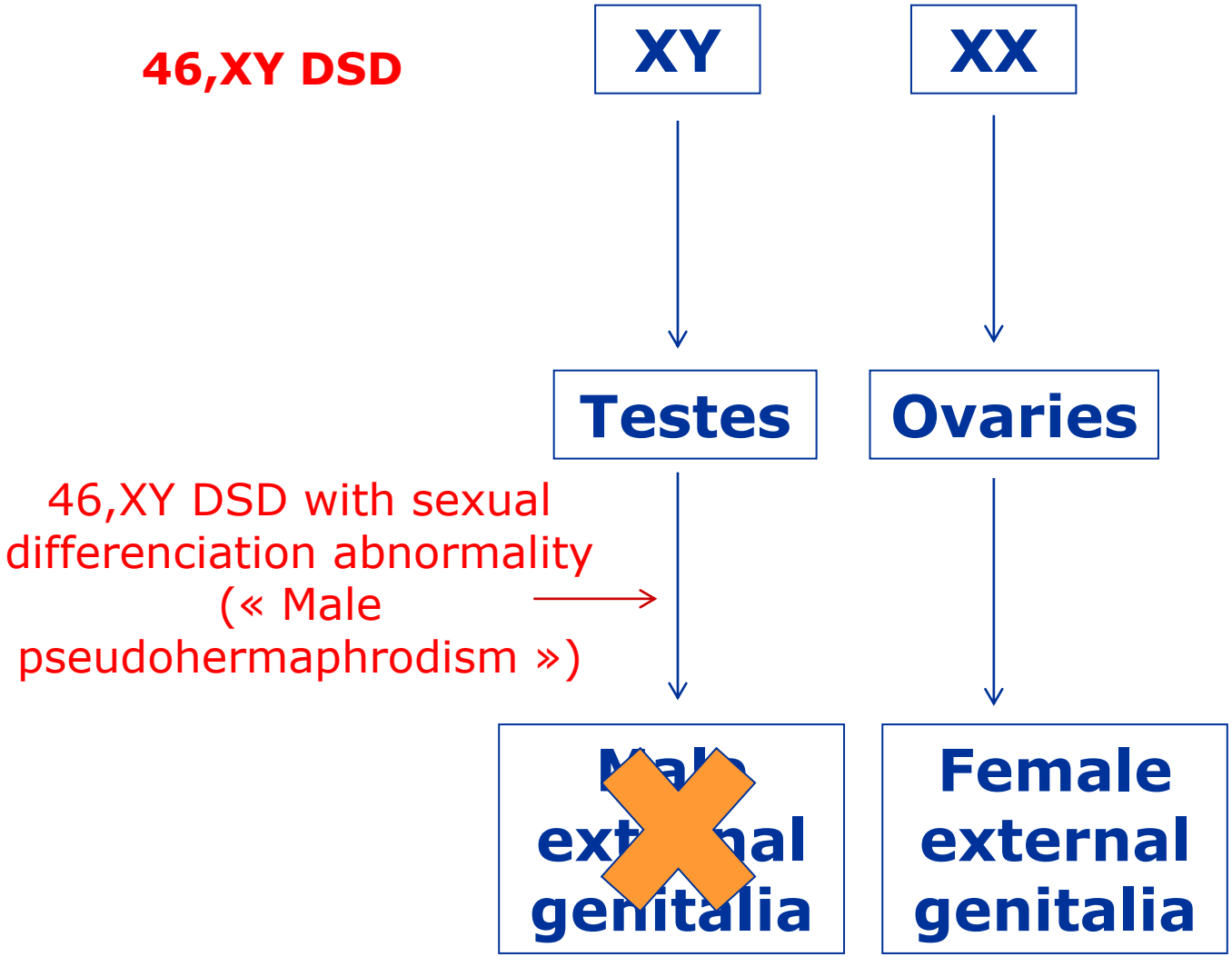
Variable phenotype, depending of the gestational age at testicular regression

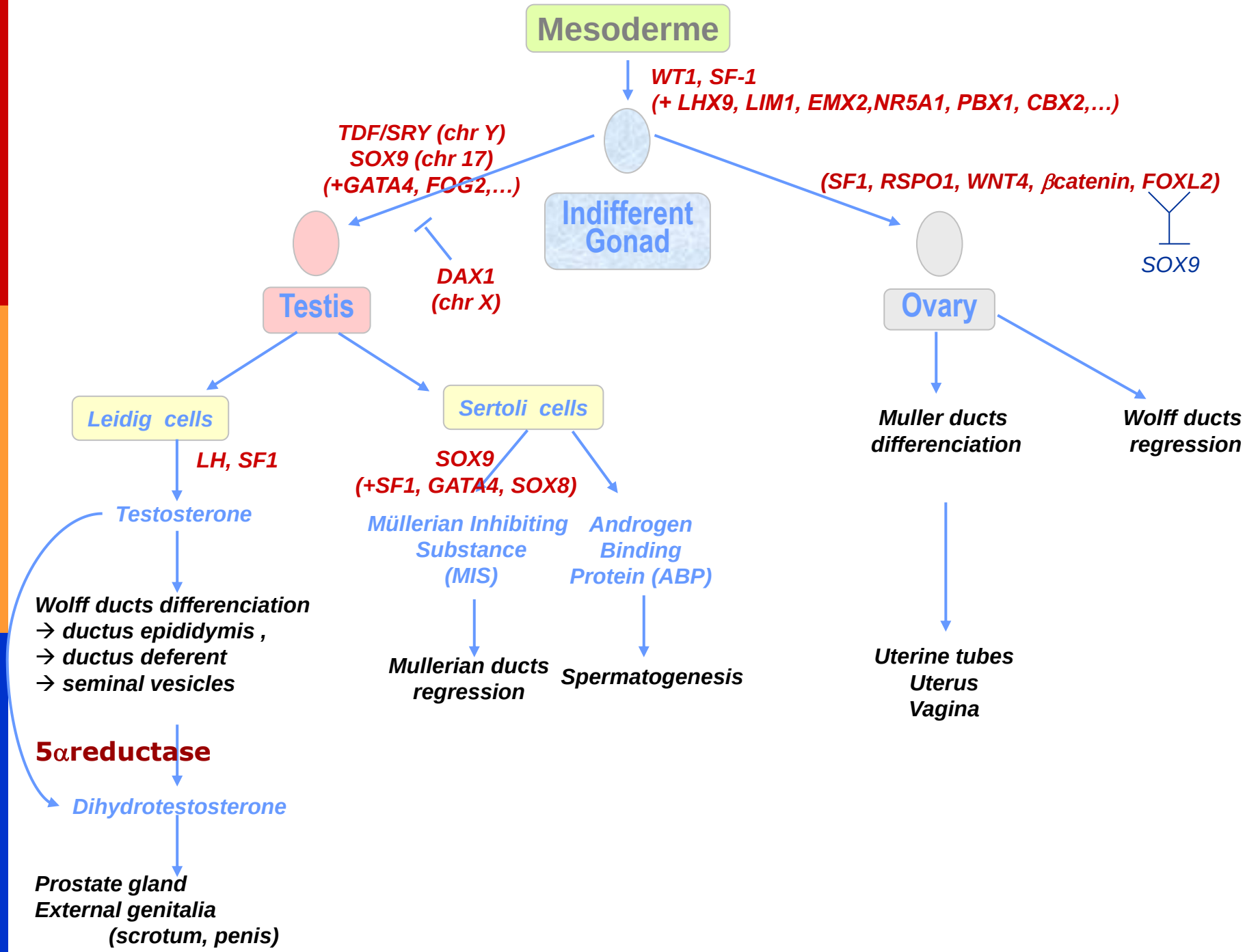
2. 46,XY DSD with sexual differenciation abnormality (Male Pseudohermaphrodism)

-46,XY

- Testes
- Female external genitalia (or ambiguous)

46,XY DSD


XY
XX
Testes
Ovaries
46,XY DSD with sexual differenciation abnormality (« Male pseudohermaphrodism »)
Male external genitalia
Female external genitalia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WT1, SF-1
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TDF/SRY (chr Y)
SOX9 (chr 17)
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Indifferent Gonad
SOX9
DAX1
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Testis
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Leidig cells
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Mullerian ducts regression
Spermatogenesis
Uterine tubes
Uterus
Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

- **Androgen insensitivity syndrome**

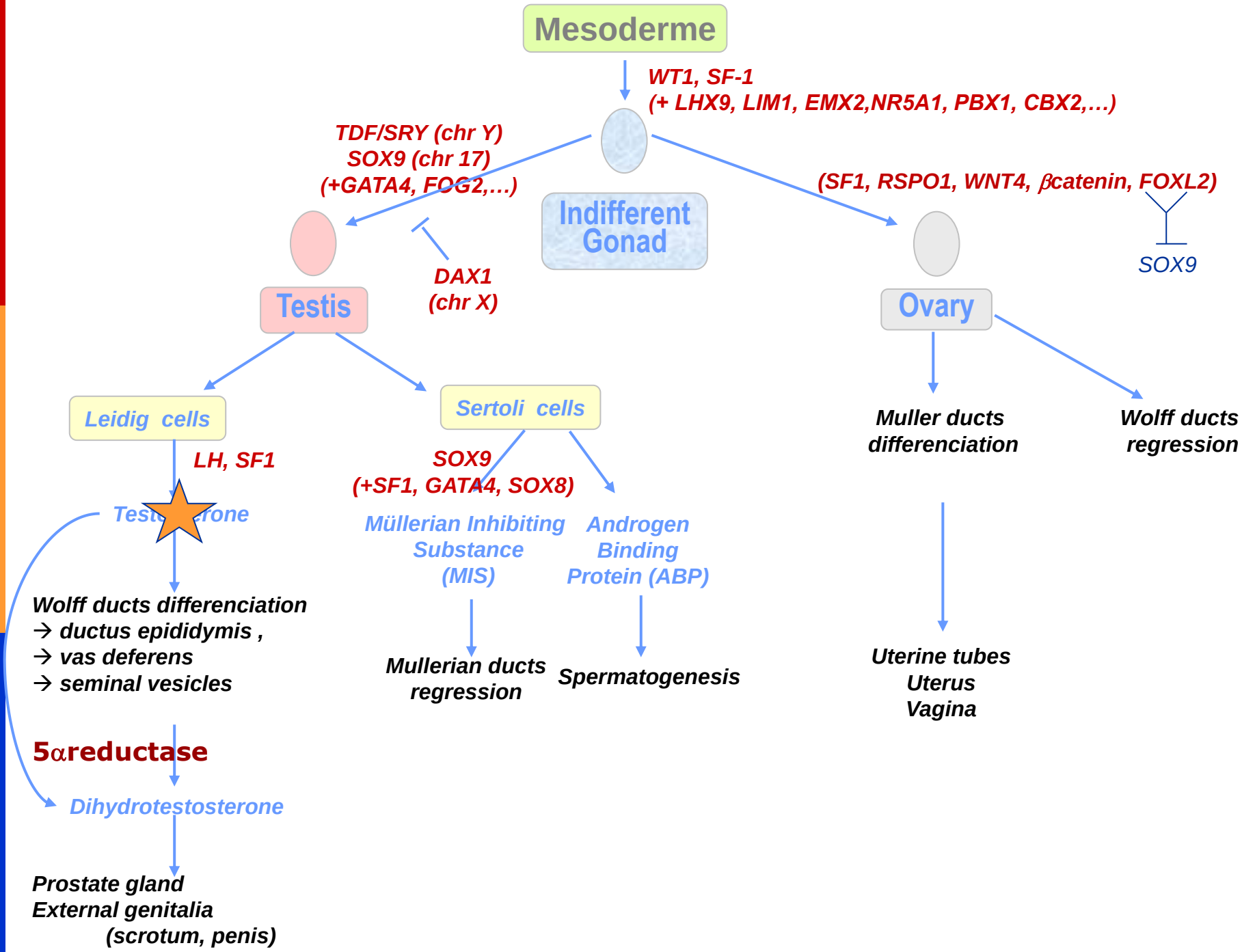
  (Mutation of the androgen receptor)

- **Testosterone deficiency**

  (Mutation of the LH receptor, Smith Lemli Opitz syndrome,…)

- **Di-OH-testosterone deficiency**

  (Mutation of the 5-α-reductase gene)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Indifferent Gonad
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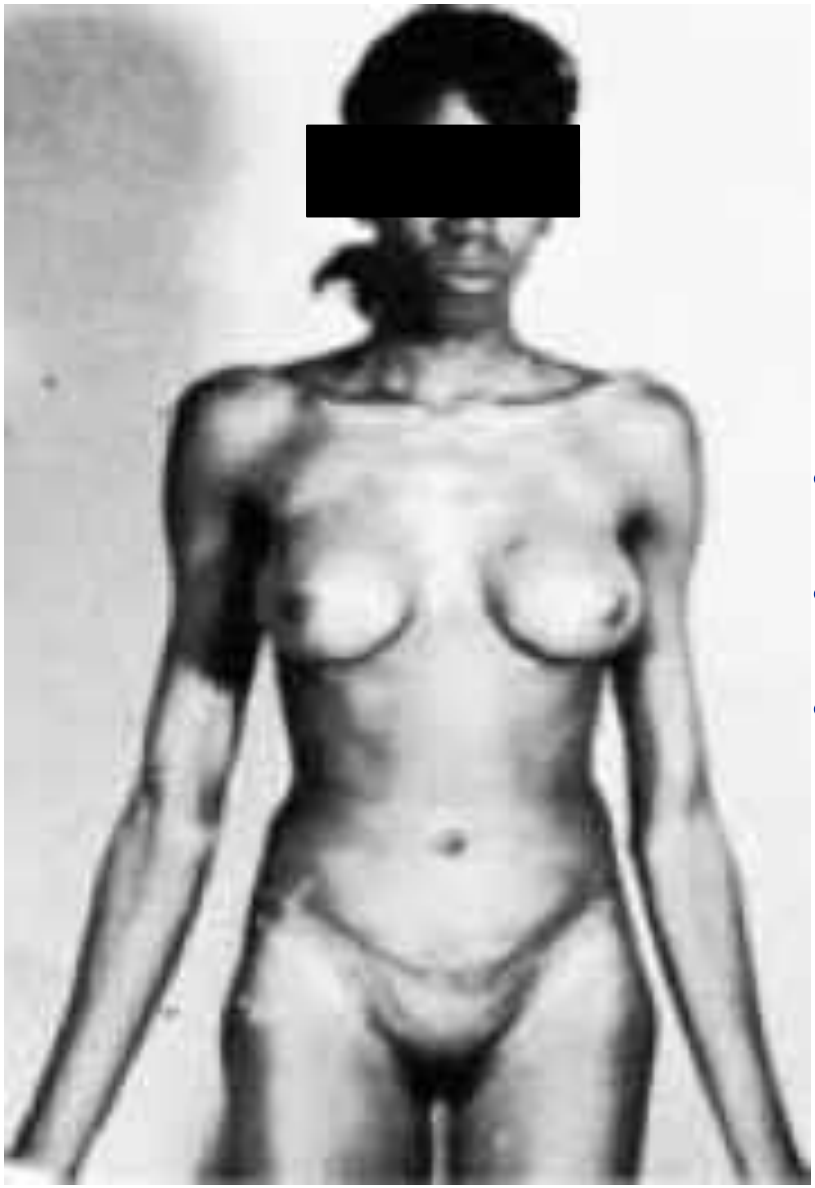
Spermatogenesis
Uterine tubes
Uterus
Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

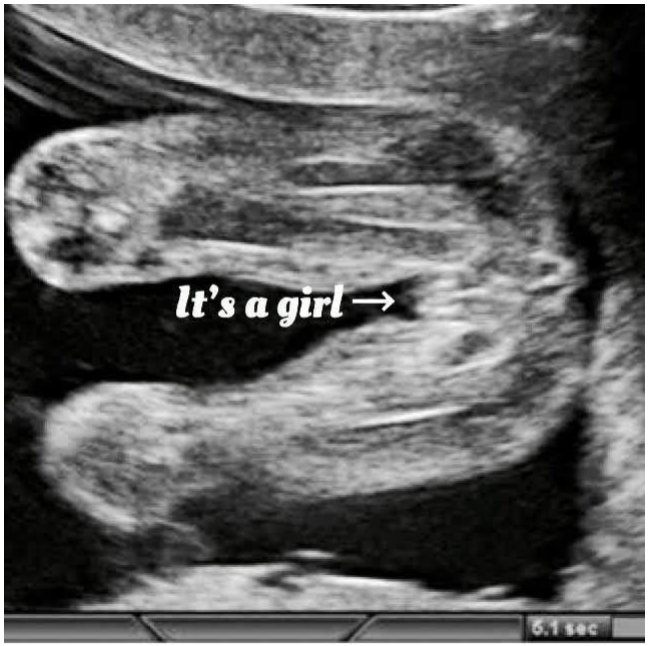
Androgen insensitivity syndrome



- 46,XY
- Testes
- Female external phenotype (blind vagina)

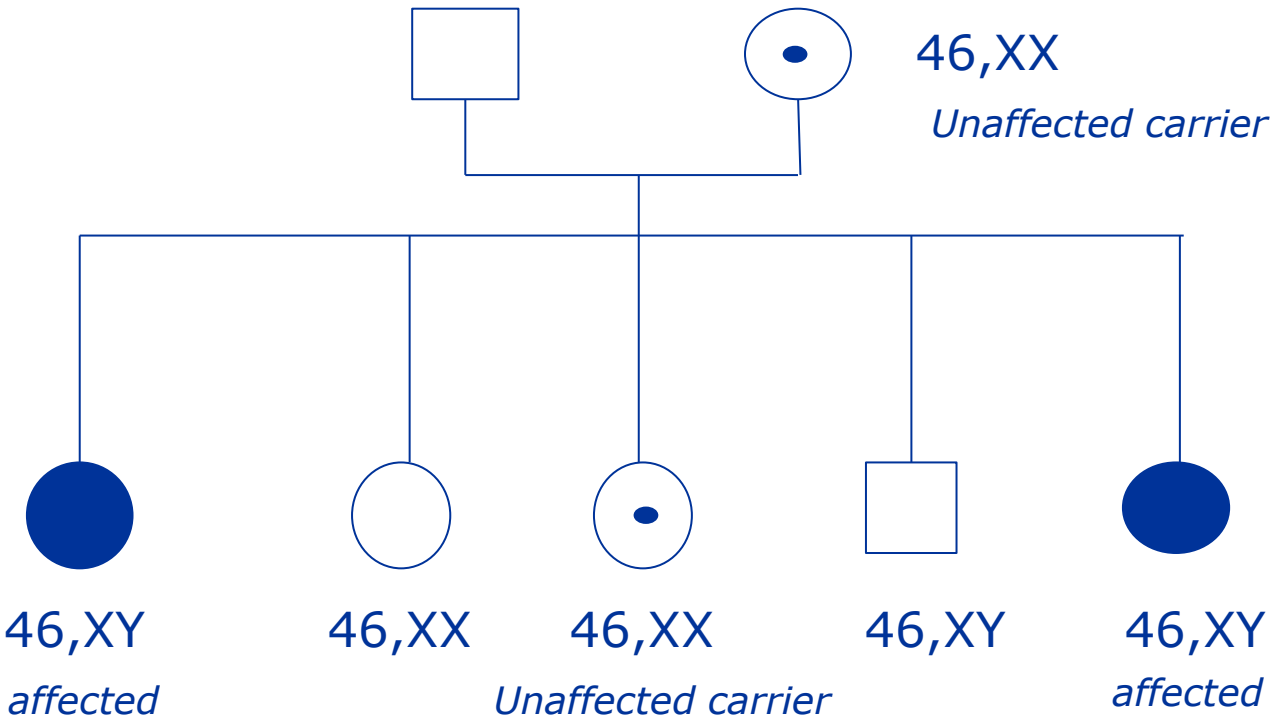
Androgen insensitivity syndrome

≠



NIPT:
46, XY

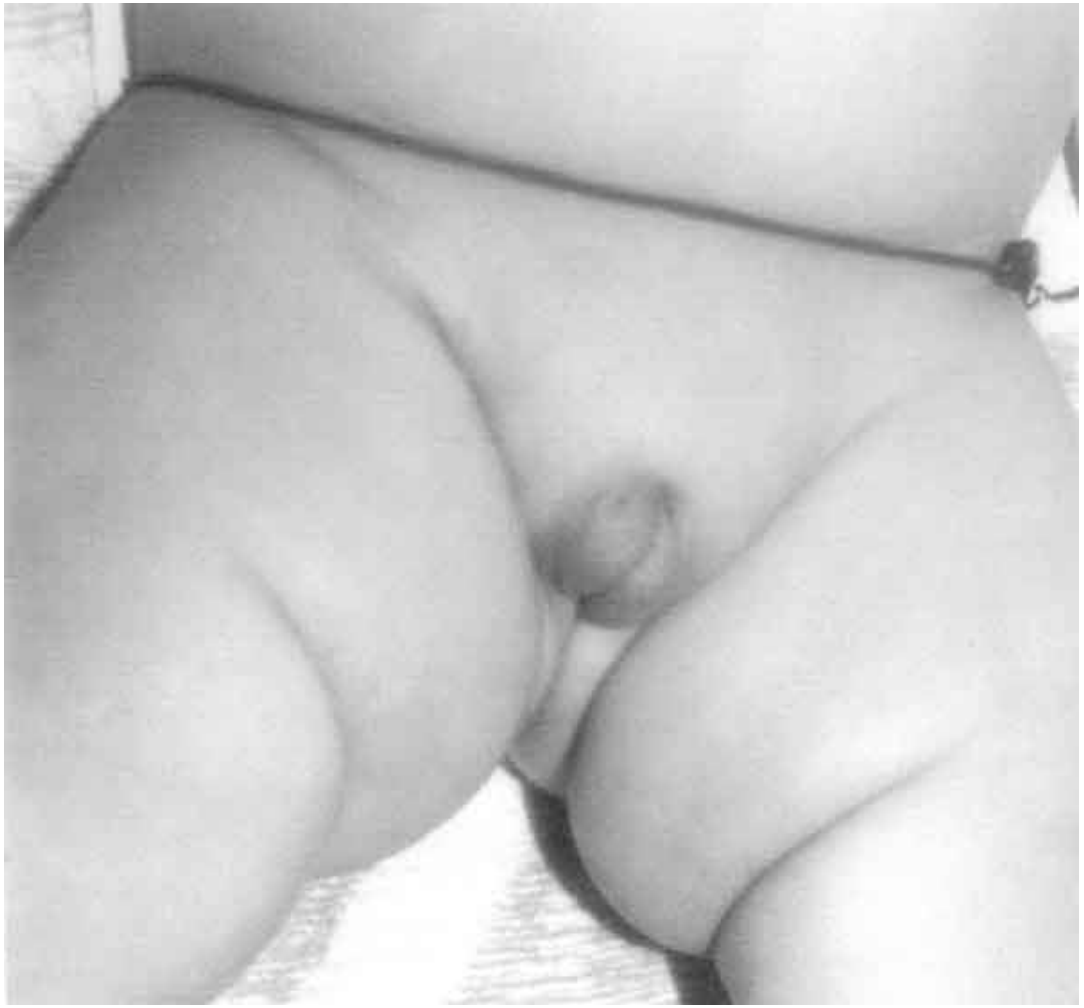
Fetal US:
female phenotype



AR gene, located on the X chromosome

Testosterone deficiency

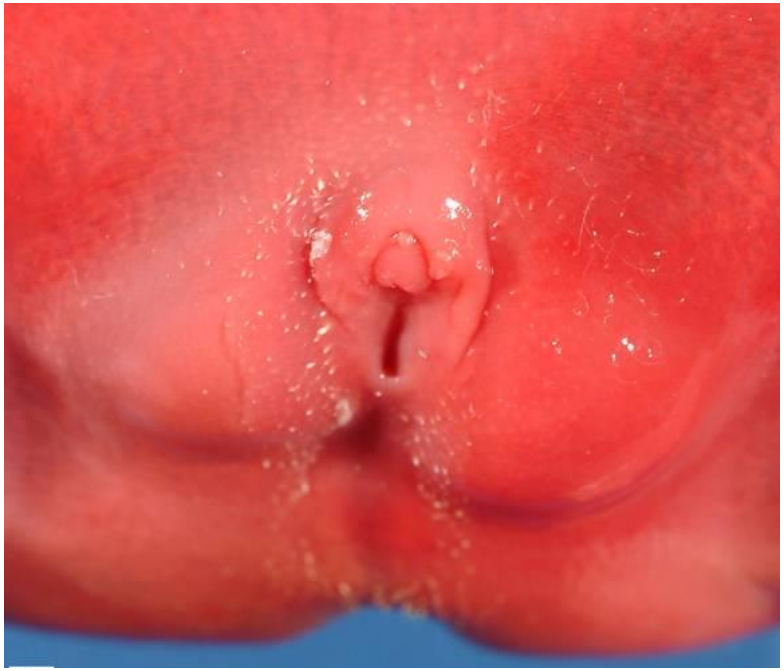
(resistance to LH hormone)

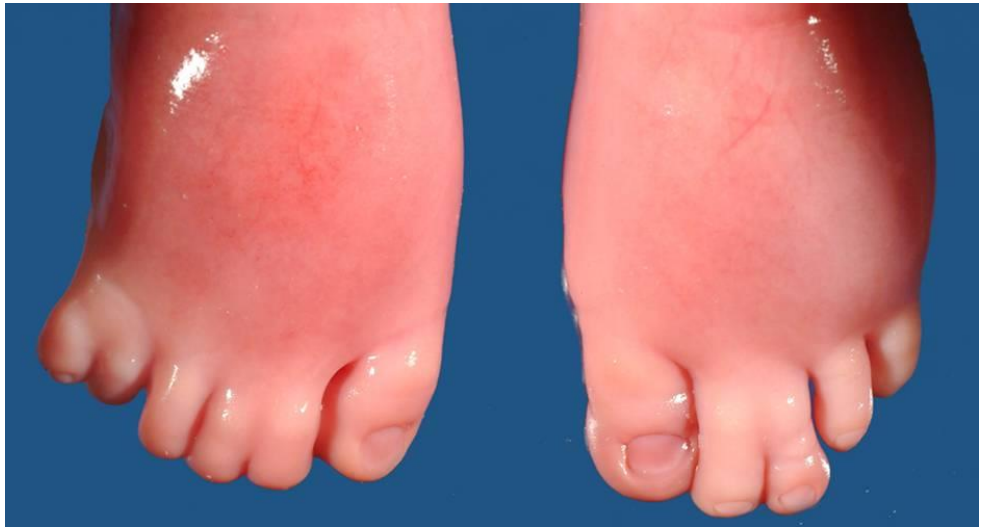


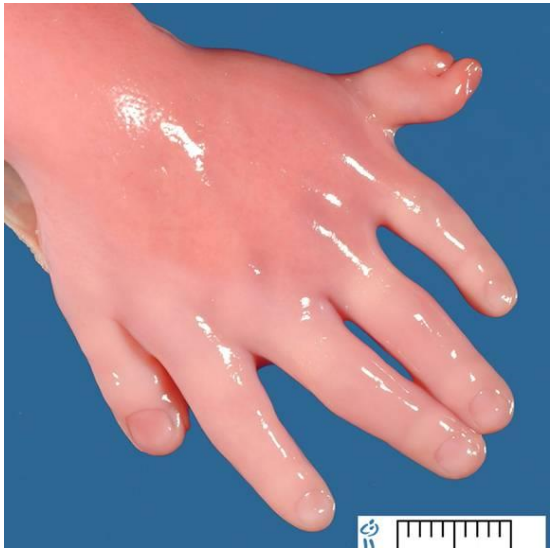
- 46,XY
- Testes
- Female external phenotype (blind vagina)

Testosterone deficiency

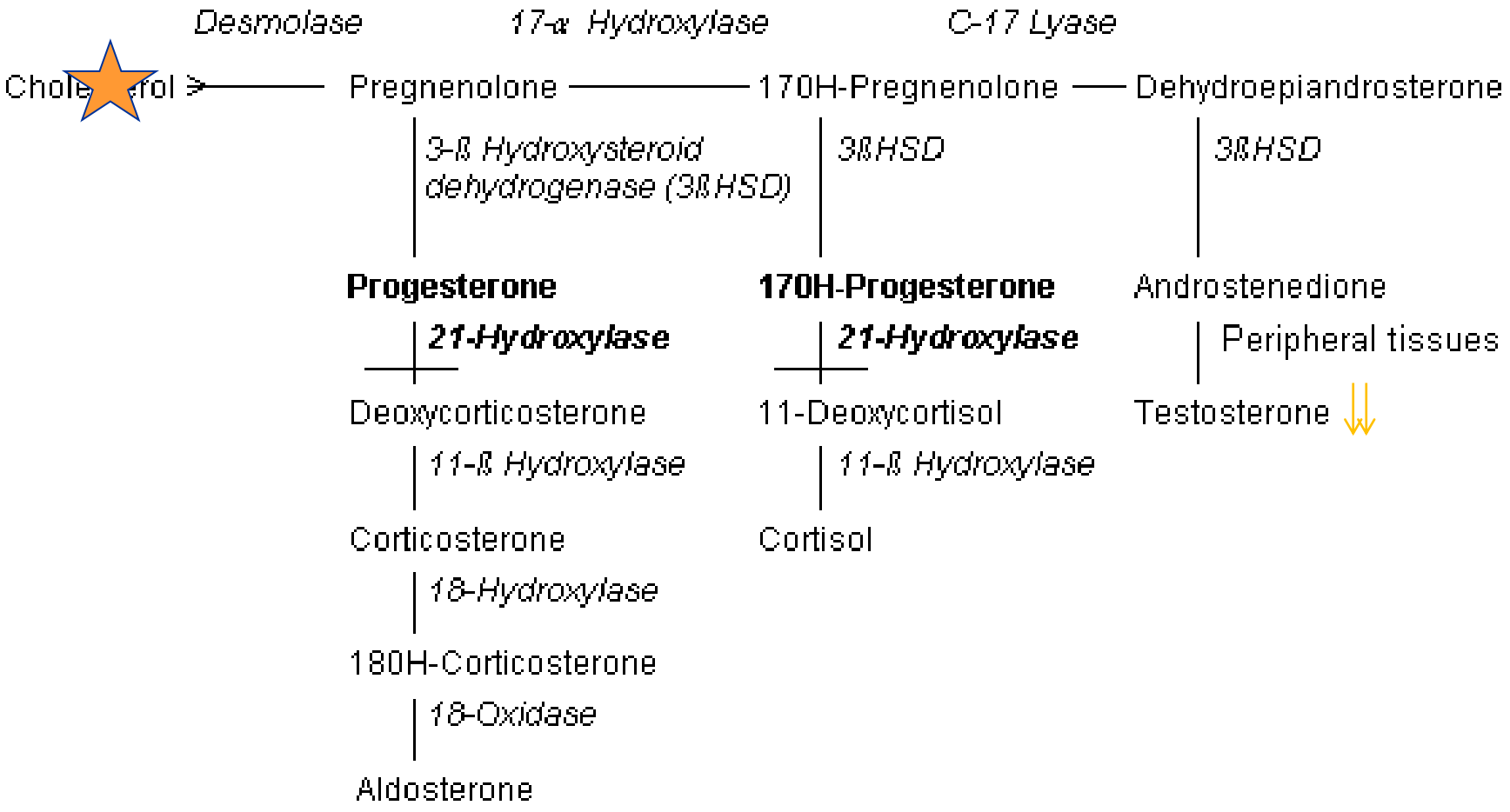
(Smith Lemli Opitz syndrome)

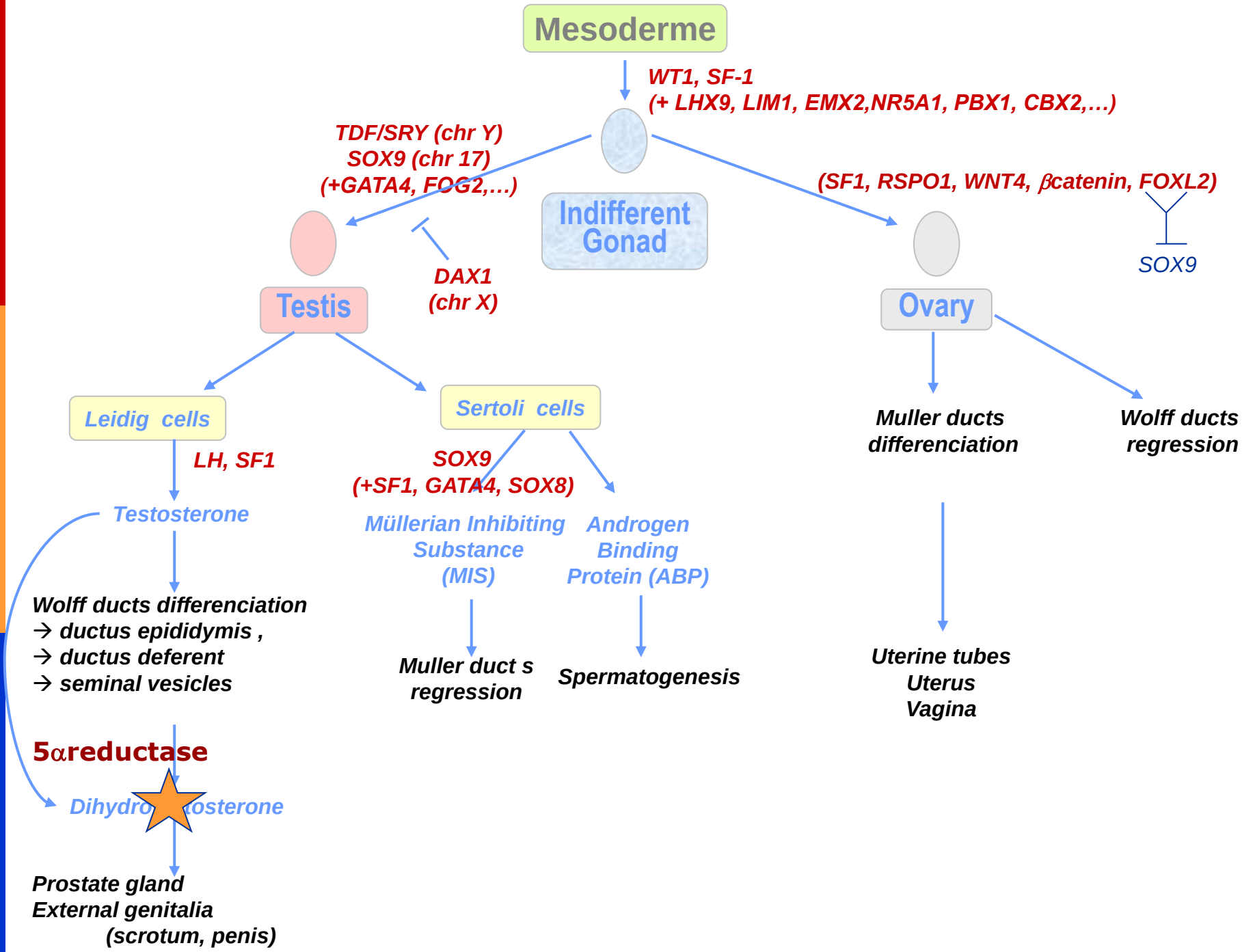






- 46,XY
- Testes
- Female external phenotype


Desmolase
17-α Hydroxylase
C-17 Lyase
Cholesterol
Pregnenolone
17OH-Pregnenolone
Dehydroepiandrosterone
3-ß Hydroxysteroid dehydrogenase (3ßHSD)
3ßHSD
3ßHSD
Progesterone
17OH-Progesterone
Androstenedione
21-Hydroxylase
21-Hydroxylase
Peripheral tissues
Deoxycorticosterone
11-Deoxycortisol
Testosterone
11-ß Hydroxylase
11-ß Hydroxylase
Corticosterone
Cortisol
18-Hydroxylase
18OH-Corticosterone
18-Oxidase
Aldosterone


Mesoderme
WT1, SF-1
(+ LHX9, LIM1, EMX2,NR5A1, PBX1, CBX2,…)
TDF/SRY (chr Y)
SOX9 (chr 17)
(+GATA4, FOG2,…)
Indifferent Gonad
(SF1, RSPO1, WNT4, βcatenin, FOXL2)
SOX9
DAX1
(chr X)
Testis
Ovary
Leidig cells
Sertoli cells
LH, SF1
SOX9
(+SF1, GATA4, SOX8)
Testosterone
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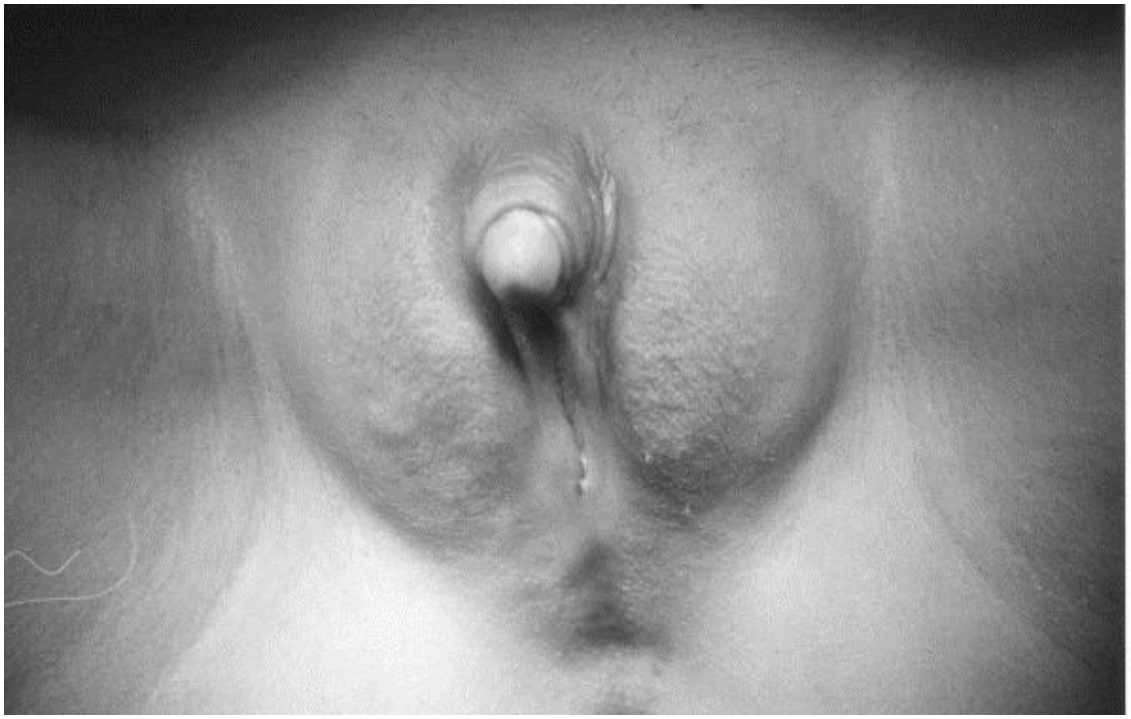
Wolff ducts regression
Wolff ducts differenciation
→ ductus epididymis ,
→ ductus deferent
→ seminal vesicles
Muller duct s regression
Spermatogenesis
Uterine tubes
Uterus
Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

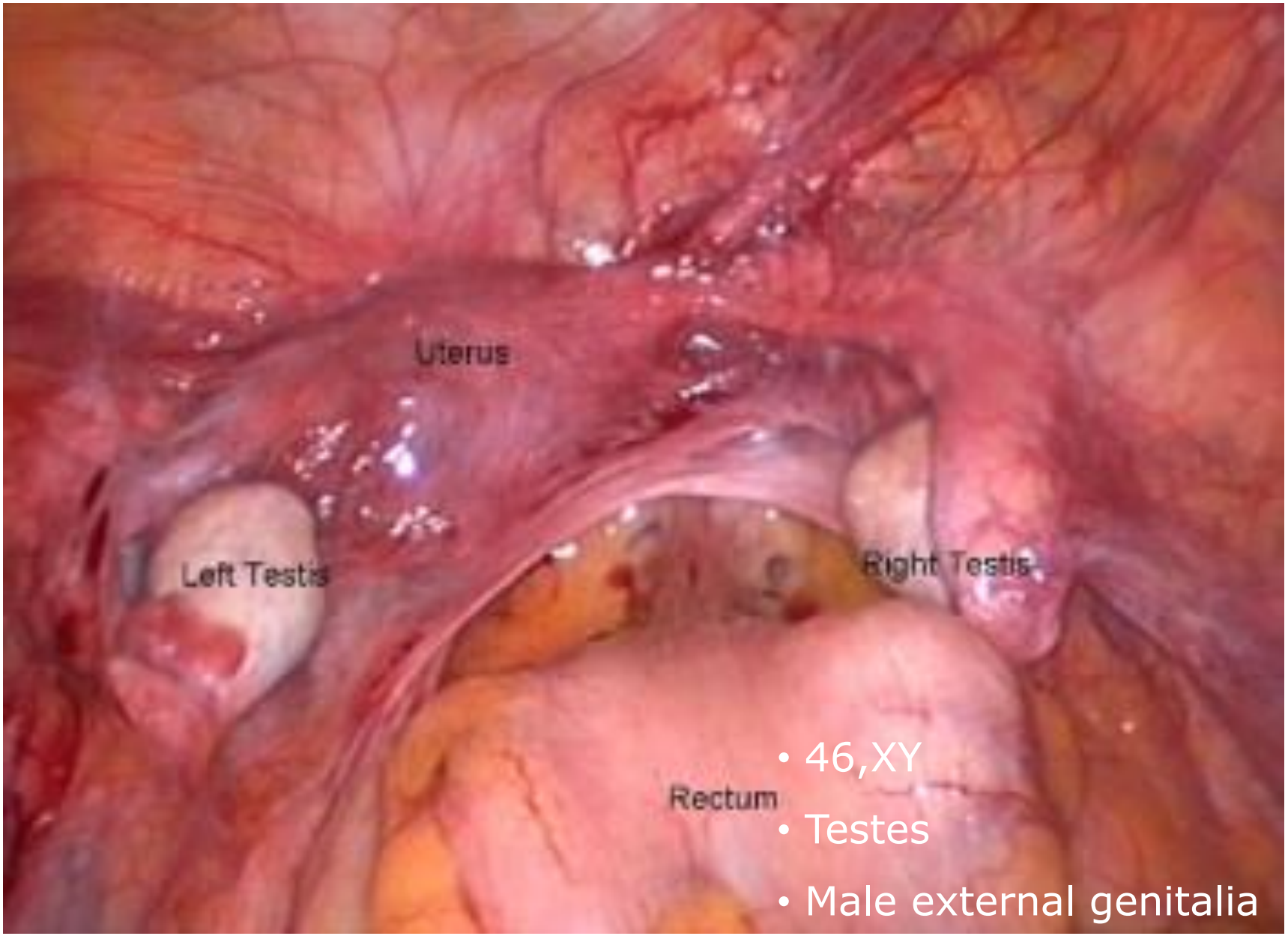
5α Reductase deficiency



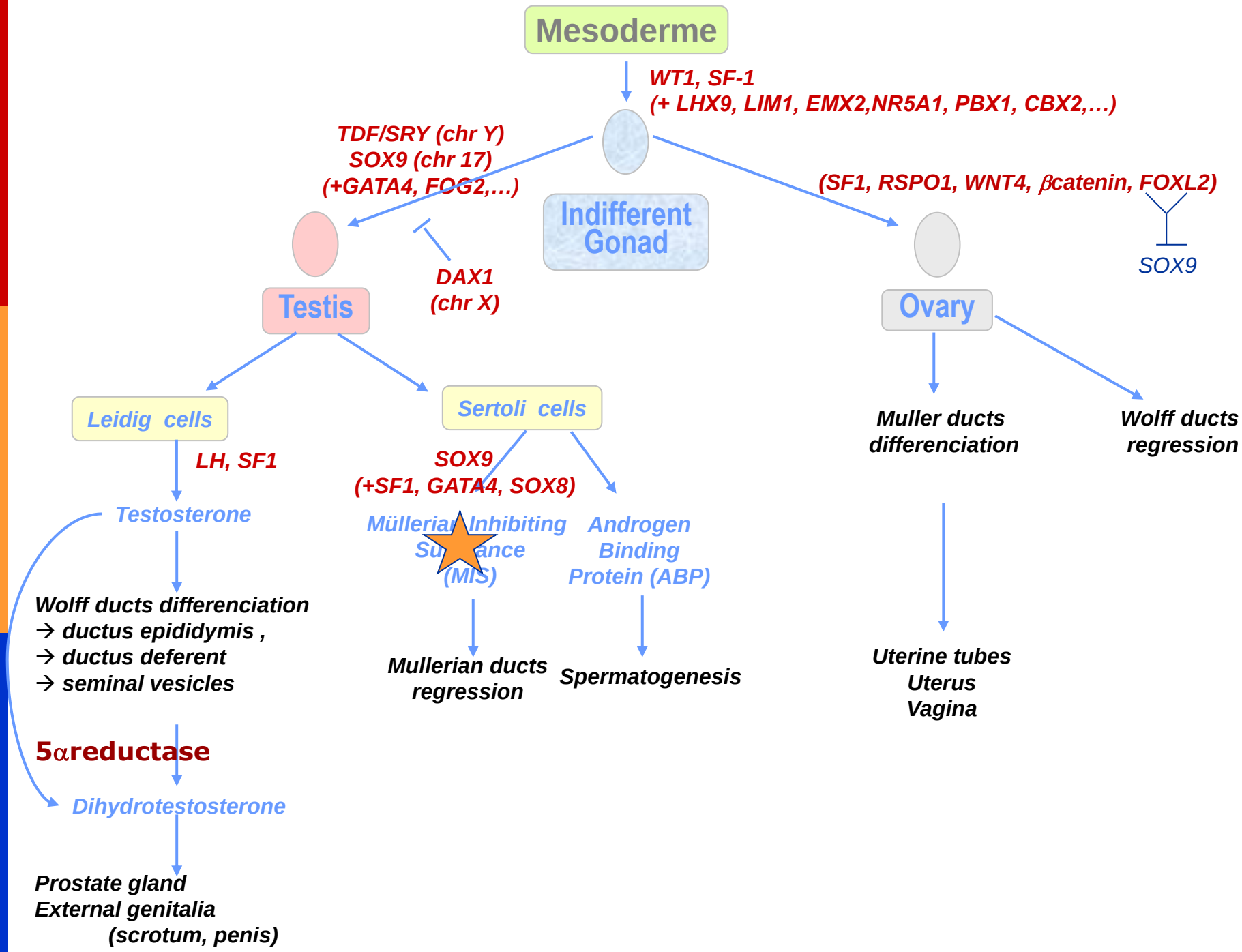
- 46,XY
- Testes
- Presence of ductus epididymitis, vas deferens, seminal vesicles
- Female external phenotype (ambiguous)

Possibility of spontaneous improvement at puberty

Rem: MIS deficiency> persistance of Mullerian residues



- 46,XY
- Testes
- Male external genitalia


Mesoderme
WT1, SF-1
(+ LHX9, LIM1, EMX2,NR5A1, PBX1, CBX2,…)
TDF/SRY (chr Y)
SOX9 (chr 17)
(+GATA4, FOG2,…)
(SF1, RSPO1, WNT4, βcatenin, FOXL2)
Indifferent Gonad
SOX9
DAX1
(chr X)
Testis
Ovary
Leidig cells
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Wolff ducts regression
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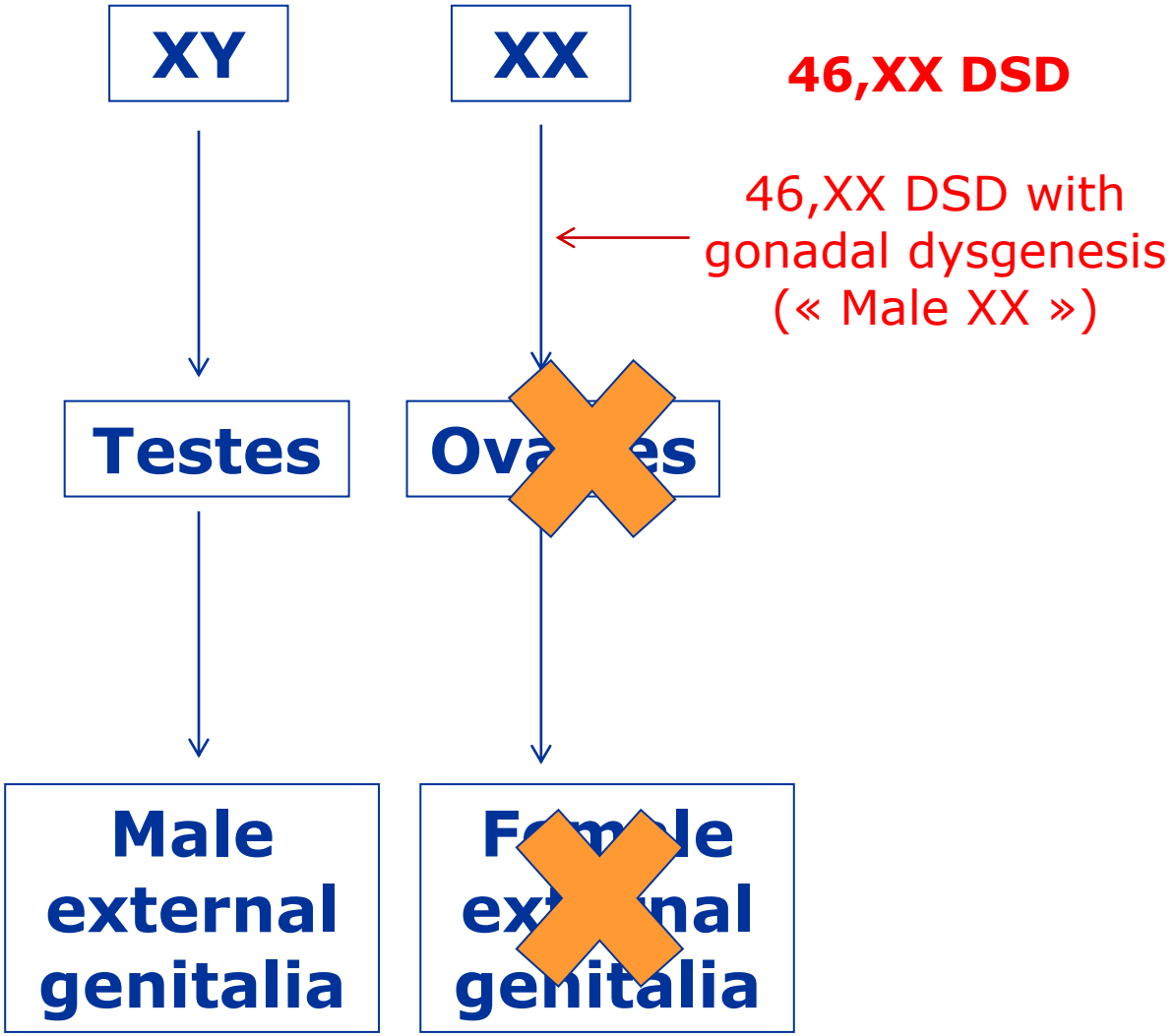
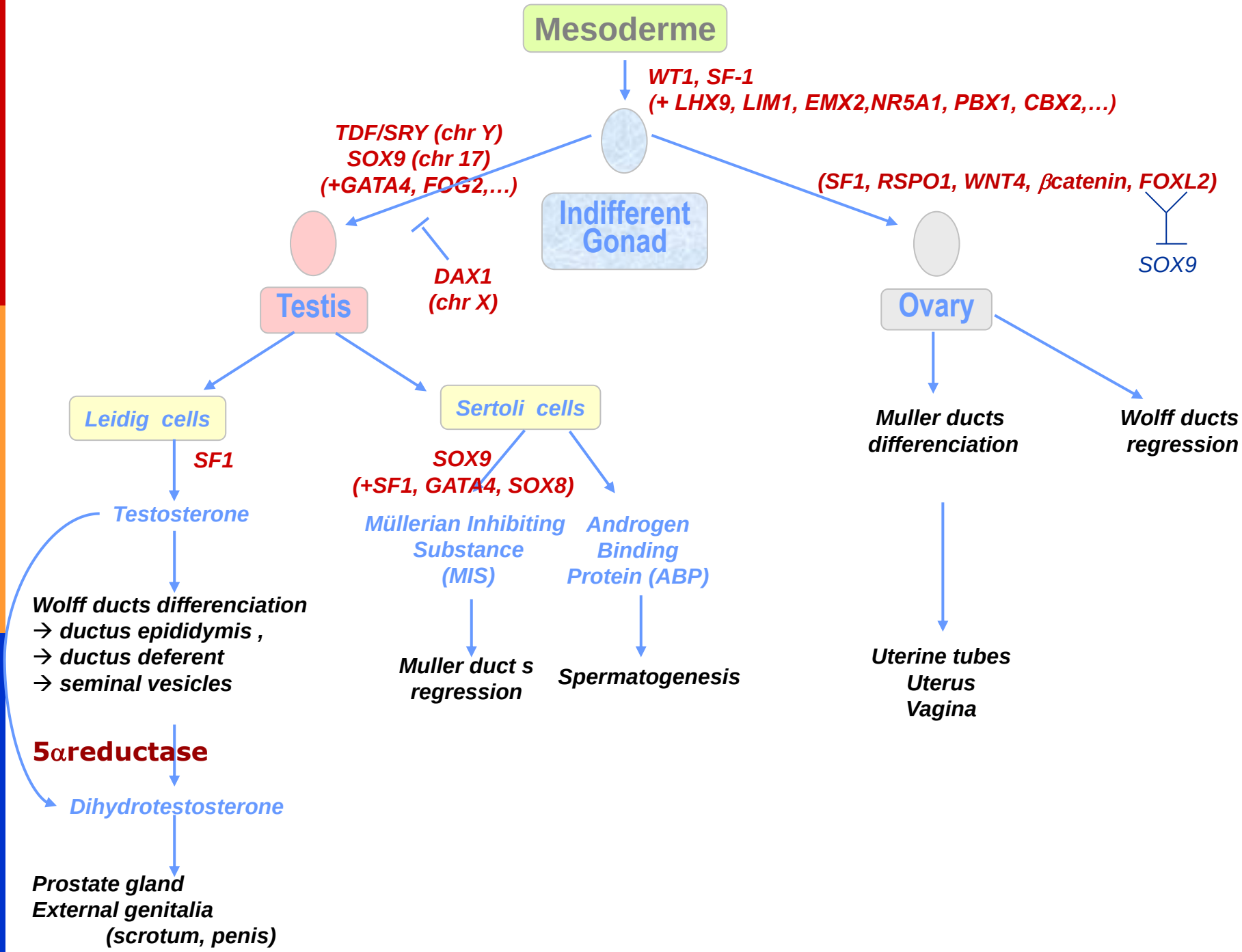
→ seminal vesicles
Mullerian ducts regression
Spermatogenesis
Uterine tubes
Uterus
Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

3. 46,XX DSD with gonadal dysgenesis (Male XX)

-46,XX

- Gonadal dysgenesis
- Male external genitalia (or ambiguous)


XY
XX
46,XX DSD
46,XX DSD with gonadal dysgenesis (« Male XX »)
Testes
Male external genitalia


Mesoderme
WT1, SF-1
(+ LHX9, LIM1, EMX2,NR5A1, PBX1, CBX2,…)
TDF/SRY (chr Y)
SOX9 (chr 17)
(+GATA4, FOG2,…)
(SF1, RSPO1, WNT4, βcatenin, FOXL2)
Indifferent Gonad
SOX9
DAX1
(chr X)
Testis
Ovary
Leidig cells
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Muller ducts differenciation
Wolff ducts regression
SF1
SOX9
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Testosterone
Müllerian Inhibiting Substance (MIS)
Androgen Binding Protein (ABP)
Wolff ducts differenciation
→ ductus epididymis ,
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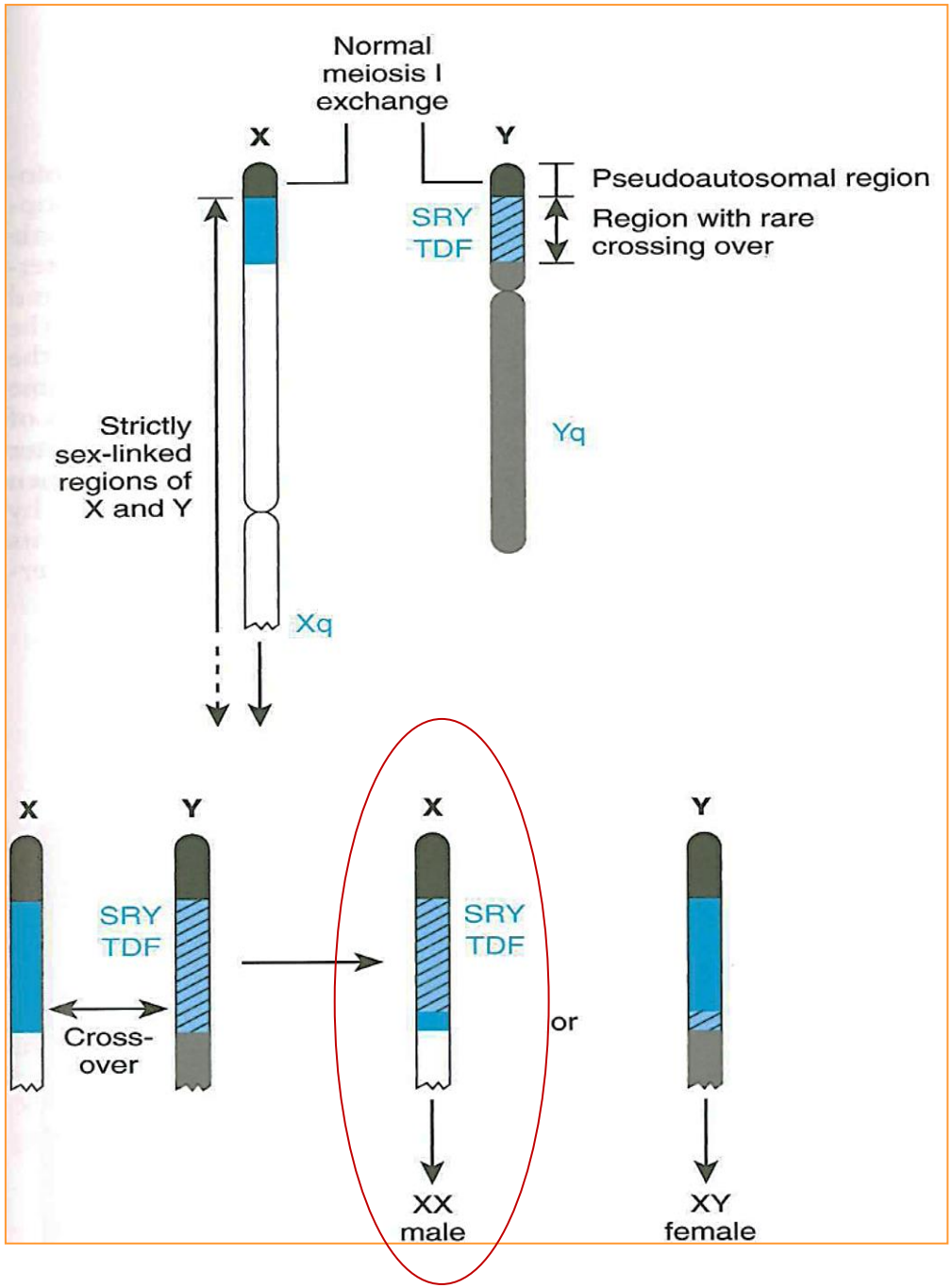
Muller duct s regression
Spermatogenesis
Uterine tubes
Uterus
Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

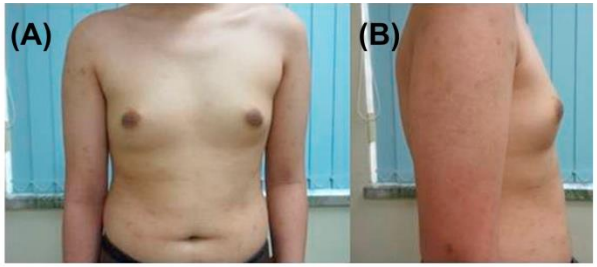
- SRY Translocation on the X chromosome
- SOX9 Duplication

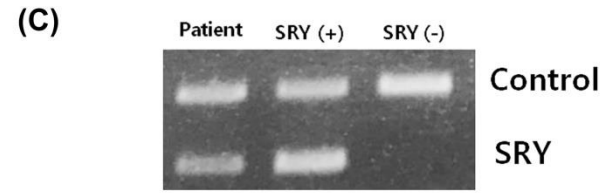


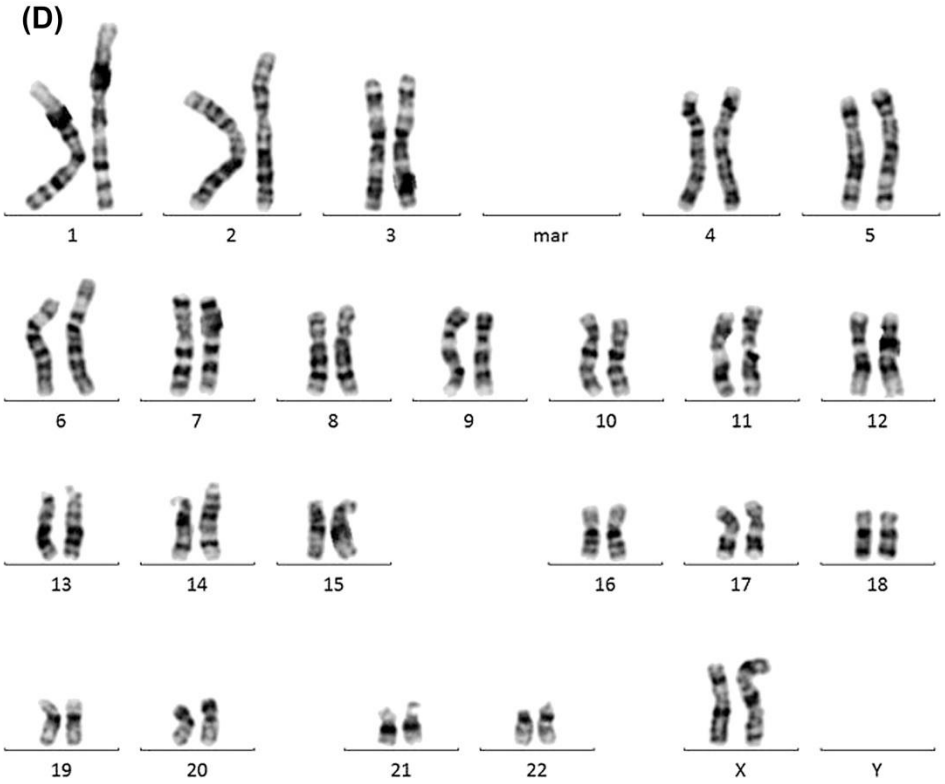
SRY = TDF
(testis-determining factor)

If genetic recombination outside the pseudoautosomic region (incidence 1/20000):

- **XX male (with the SRY gene on a X chromosome)**
- XY female (without the SRY gene on the Y chromosome)

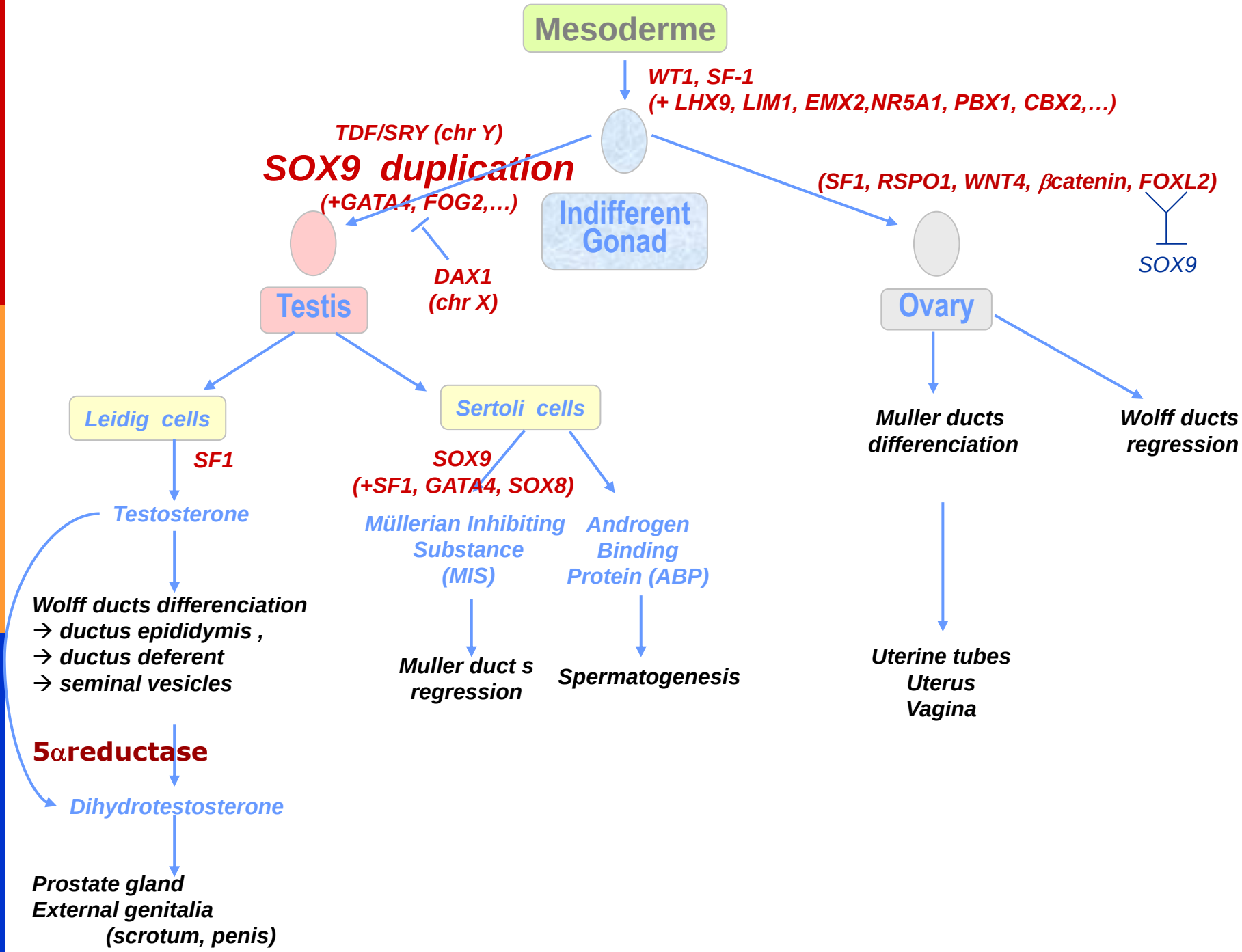






Patient with:
- Gynecomastia
- Hypergonadotropic hypogonadism

Min et al, Pediatrics and Neonatology 2015


Mesoderme
WT1, SF-1
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TDF/SRY (chr Y)
SOX9 duplication
(+GATA4, FOG2,…)
DAX1
(chr X)
Indifferent Gonad
(SF1, RSPO1, WNT4, βcatenin, FOXL2)
SOX9
Testis
Ovary
Leidig cells
Sertoli cells
SF1
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Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

RBM ONLINE

ELSEVIER

Article

Duplication of *SOX9* associated with 46,XX ovotesticular disorder of sex development

Berenice López-Hernández [a], *Juan Pablo Méndez* [b], *Ramón Mauricio Coral-Vázquez* [c,d], *Jesús Benítez-Granados* [b], *Juan Carlos Zenteno* [e], *Vanessa Villegas-Ruiz* [e], *Raúl Calzada-León* [f], *Daniela Soderlund* [g], *Patricia Canto* [b,*]

nature COMMUNICATIONS

ARTICLE

Corrected: Publisher Correction

https://doi.org/10.1038/s41467-018-07784-9 OPEN

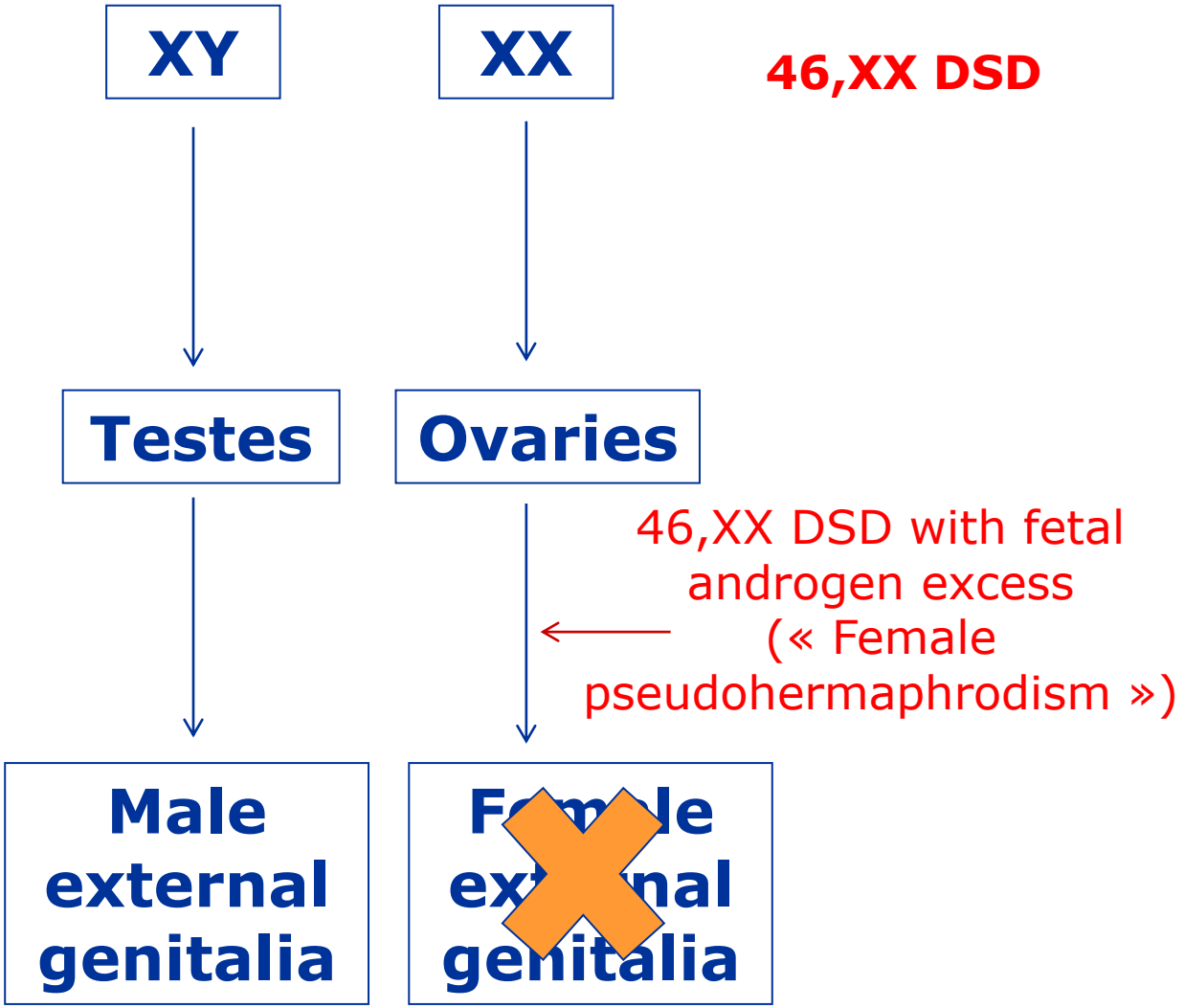
Human sex reversal is caused by duplication or deletion of core enhancers upstream of *SOX9*

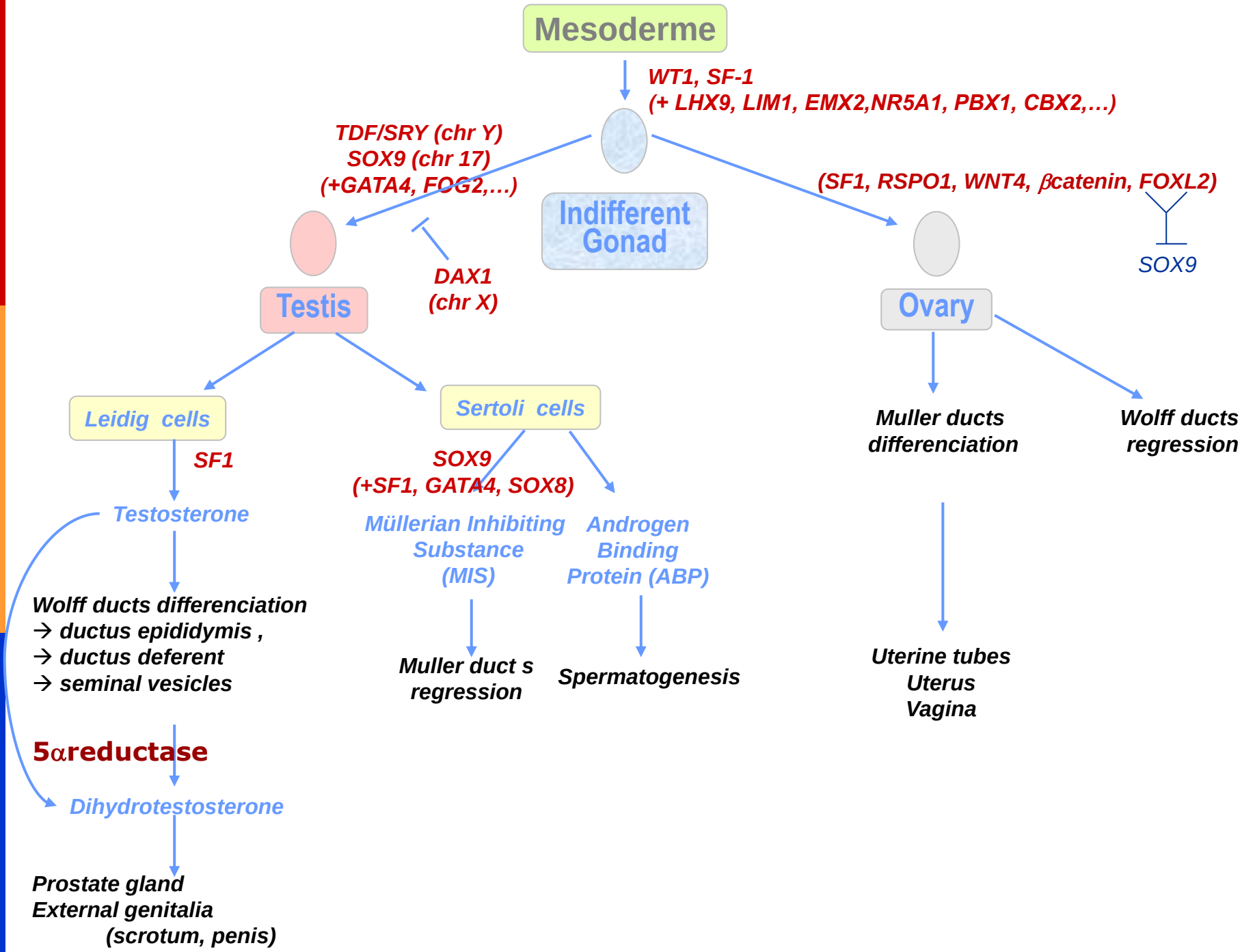
Brittany Croft[1,2], Thomas Ohnesorg[1,3], Jacqueline Hewitt[1,4,5], Josephine Bowles[6,7], Alexander Quinn[7], Jacqueline Tan[1], Vincent Corbin[8], Emanuele Pelosi[7], Jocelyn van den Bergen[1], Rajini Sreenivasan[1,9], Ingrid Knarston[1,3], Gorjana Robevska[1], Dung Chi Vu[10], John Hutson[1,3,11], Vincent Harley[9], Katie Ayers[1,3], Peter Koopman[7] & Andrew Sinclair[1,3]

4. 46,XX DSD with fetal androgen excess (Female Pseudohermaphrodism)

-46,XX

- Ovaries
- Male external genitalia (or ambiguous)


XY
XX
46,XX DSD
Testes
Ovaries
46,XX DSD with fetal androgen excess (« Female pseudohermaphrodism »)
Male external genitalia
Female external genitalia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TDF/SRY (chr Y)
SOX9 (chr 17)
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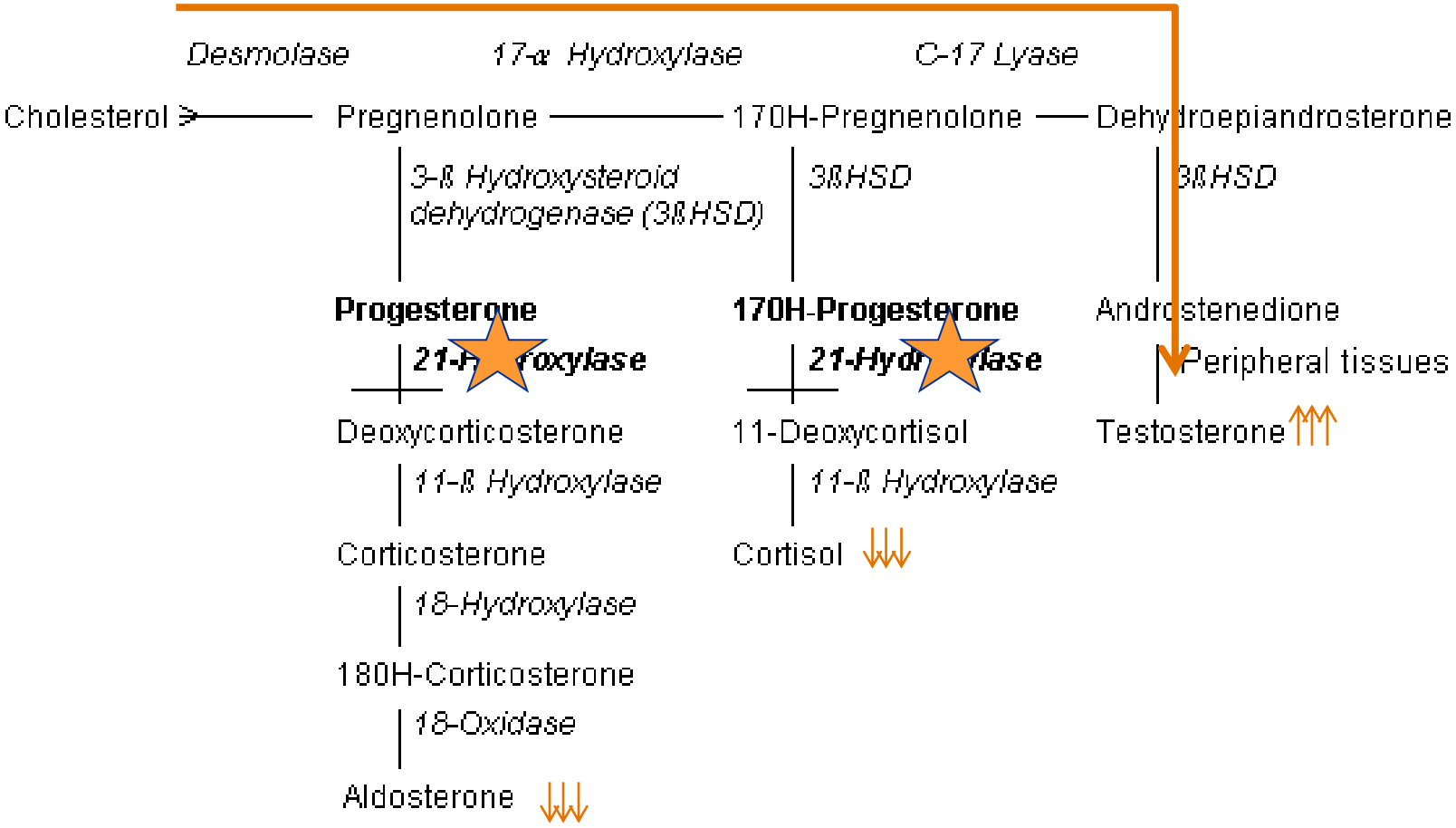
Uterine tubes
Uterus
Vagina
5αreductase
Dihydrotestosterone
Prostate gland
External genitalia
(scrotum, penis)

- Early exposition to androgens
  - Congenital adrenal hyperplasia
  - Maternal adrenal tumor
  - Placental tumor
  - Exogenous maternal androgene treatment
  - Aromatase deficiency (androgens > estrogens)
  - Etc…

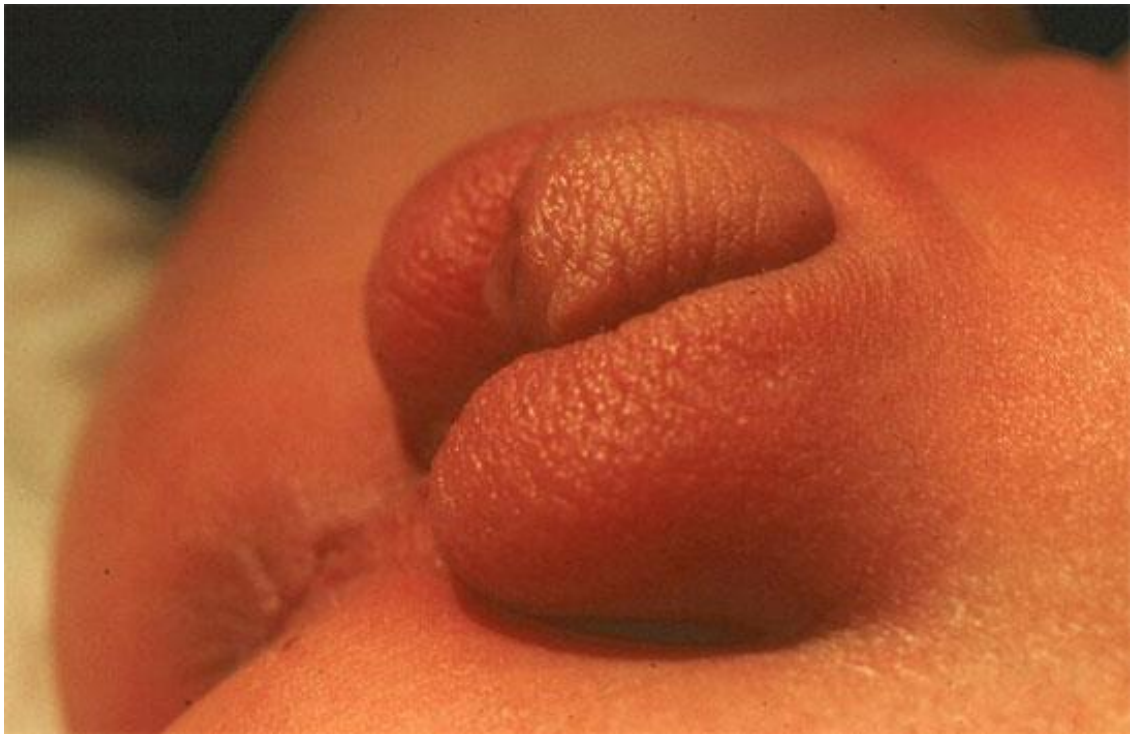
Congenital adrenal hyperplasia

(21-hydroxylase deficiency)

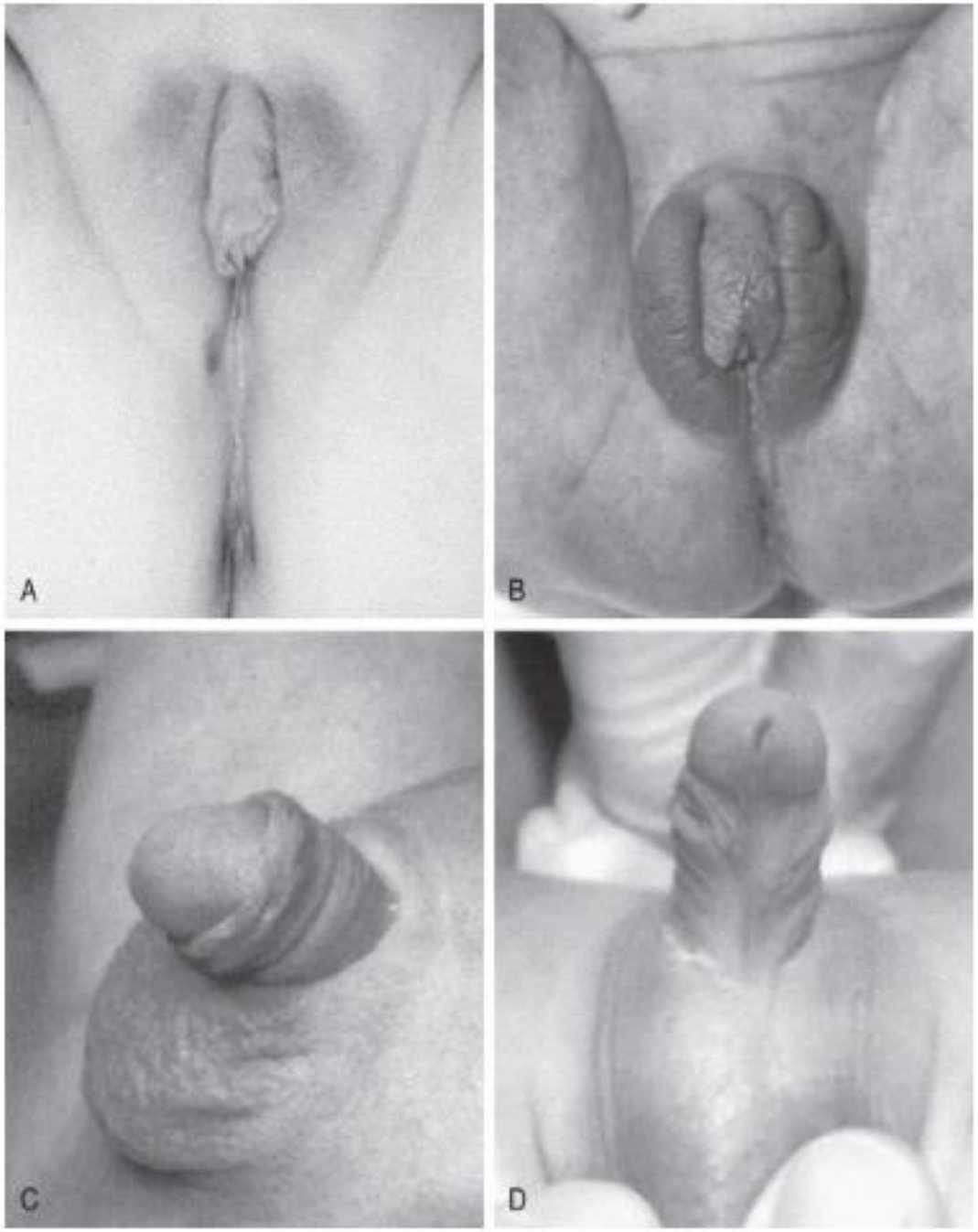


Congenital adrenal hyperplasia

(21-hydroxylase deficiency)

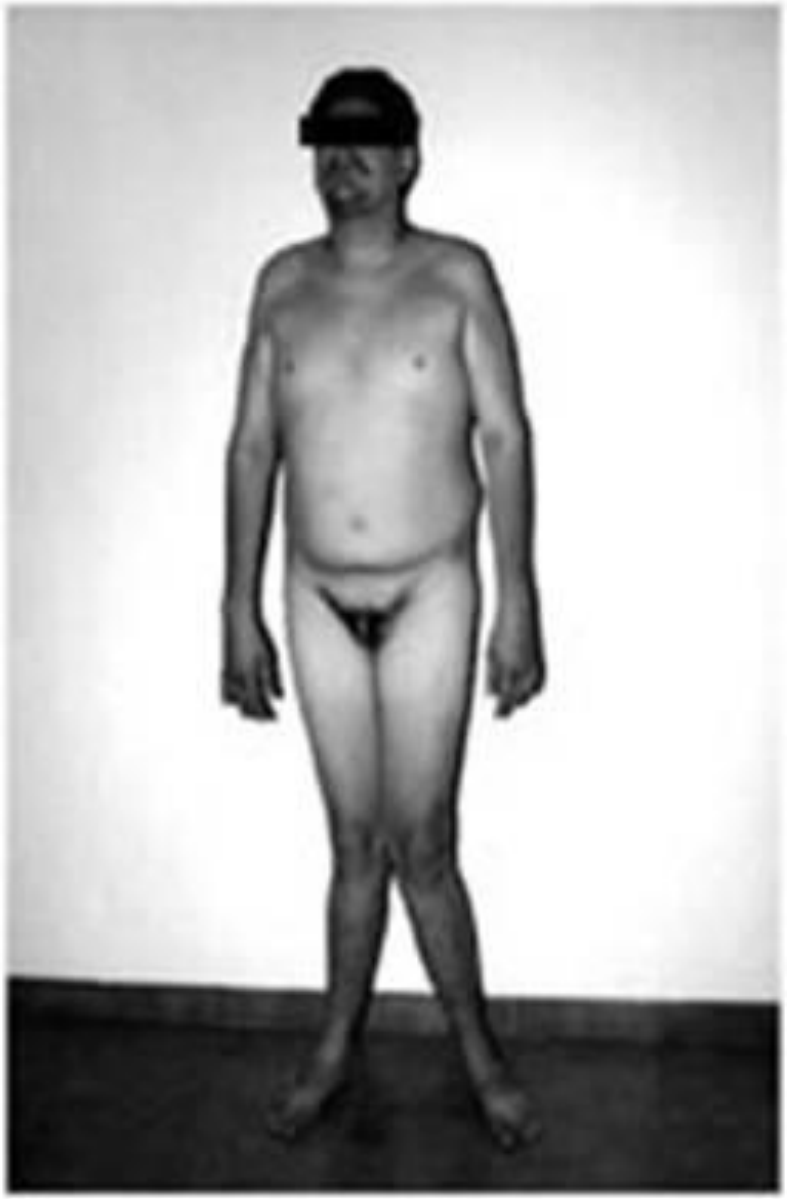


- 46,XX
- Ovaries
- Male external phenotype (ambiguous)


A
B
C
D

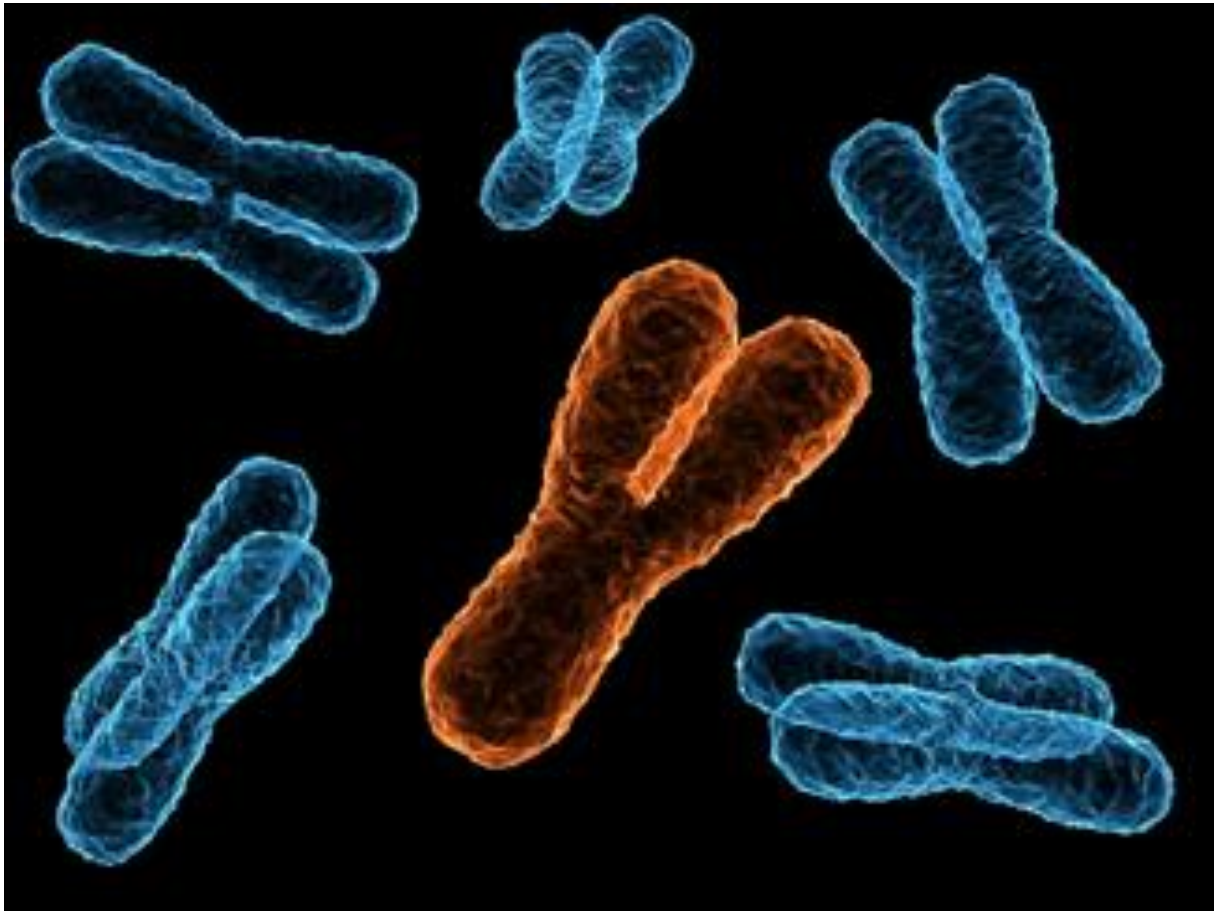
Aromatase deficiency

↑↑ (androgenes ≠ Estrogenes) ↓↓



- 46,XX
- Ovaries
- Male external phenotype (ambiguous)


Conclusion



	Etiology	Genotype	Gonades	External genitalia	Other symptoms
Sex chromosome DSD	**chimerism XX/XY (true hermaphrodism)** ***or*** **Mosaic sry-/sry+** ***or*** **?**	46,XX/46,XY (30%) *or* 46,XX (60%) *or* 46, XY (10%)	Ovotestis	Variable (female > ambiguous > male)	
	Turner	45,X *Variants:* 46,X,i(Xq) 46,X,rX mosaics	Ovarian dysgenesis	Female	Short stature, webbed neck, cubitus valgus, cardiac malformation, infertility *With small X ring: intellectual disability*
	Klinefelter	47,XXY *Variants:* 48,XXYY 48,XXXY 49,XXXXY mosaics	Testicular dysgenesis (seminiferous cords hyalinosis)	Male	Tall stature, hypogonadism, gynecomastia, infertility *With variants: intellectual disability*
	Mosaic XY/X	46,XY/45,X	Mixed gonadal dysgenesis	Variable (female > ambiguous > male)	

	Etiology	Genotype	Gonades	External genitalia	Other symptoms
46,XY DSD with gonadal dysgenesis (Female XY)	**SRY mut or del (Swyer)**	46,XY	Gonadal dysgenesis	Female	
	SOX9 mutation	46,XY	Gonadal dysgenesis	Ambiguous > Female	Skeletal dysplasia
	SF1 Mutation	46,XY *rem: 46,XX*	Gonadal dysgenesis *Ovarian insufficiency*	Ambiguous > Female (+/- utérus) *Female*	+/- adrenal insufficiency *+/- adrenal insufficiency*
	WT1 Mutation	46,XY *rem: 46,XX*	Gonadal dysgenesis *Ovarian insufficiency?*	Ambiguous > Female (+/- utérus) *Female*	Renal insufficiency and Wilms tumor (Denys-Drash) Glomerular néphropathy (Frasier) Wilms tumor, aniridia, mental retardation (WAGR) *idem*
	DAX1 duplication	46,XY	Gonadal dysgenesis	Ambiguous > Female	
46,XY DSD with sexual differenciation abnormality (Male pseudo-hermaphrodism)	**5α-réductase deficiency (diOHtestosterone deficiency)**	46,XY	Testes	Ambiguous (improvement at puberty)	
	LH receptor mutation (testostérone deficiency)	46,XY	Testes	Female (blind vagina) or ambiguous if partial deficiency	
	Androgen receptor mutation (androgen insensitivity syndrome)	46,XY	Testes	Female (blind vagina) or ambiguous if partial insensitivity	

	Etiology	Genotype	Gonades	External genitalia	Other symptoms
46,XX DSD with gonadal dysgenesis (Male XX)	**SRY translocation on the X chrom.**	46,XX	Gonadal dysgenesis	Ambiguous > Male	
	SOX9 Duplication	46,XX	Gonadal dysgenesis	Ambiguous > Male	
46,XX DSD with fetal androgen excess (Female pseudo-hermaphrodism)	**Early exposition to androgenes (congenital adrenal hyperplasia, maternal adrenal or placental tumor, exogenous androgene treatment, aromatase deficiency)**	46,XX	Ovaries	Ambiguous	

	Etiology	Genotype	Gonades	External genitalia	Other symptoms
Others	**Trisomy X**	47,XXX	Normal ovaries	Normal female	Normal phenotype (above average stature) No infertility No intellectual disability but 70% learning problems Abnormal behavior?
	Tetrasomy X	48,XXXX	Normal ovaries	Normal female	Intellectual disability
	Pentasomy X	49,XXXXX	Normal ovaries	Normal female	Intellectual disability
	XYY condition	47,XYY	Normal testes	Normal male	Normal phenotype (tall stature) No infertility No intellectual disability but 50% speech delay Attention deficit? Hyperactivity?
	MIS deficiency	46,XY	Normal testes BUT persistance of mullerian residues (uterus, upper vagina)	Normal male	No infertility No intellectual disability
	Interstital Y deletion including AZFa, AZFb or AZFc	46,XY	Normal testes BUT non obstructive azoospermia (or severe oligospermia)	Normal male	Infertility
	XY gonadal agenesis	46,XY	Embryonic testicular regression	Female > ambiguous > male	Infertility

CROMOSOMAS

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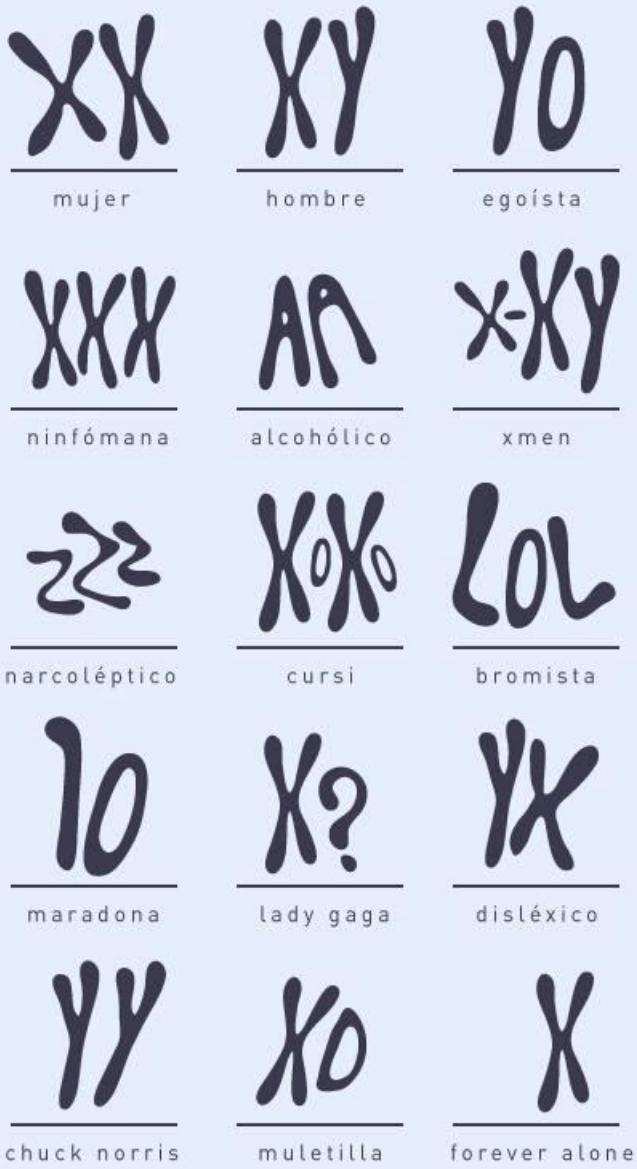

THANK YOU FOR YOUR ATTENTION