

# Androgen Insensitivity Syndrome - at a glance

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# Definition

Androgen insensitivity syndrome is an **X-linked disorder** of **absent or defective virilization** in **46,XY** individuals due to absence or deficiency of androgen action resulting from **mutations in the AR gene**.

Boehmer ALM et al. J Steroid Biochem Mol Biol 1996;58:569-75



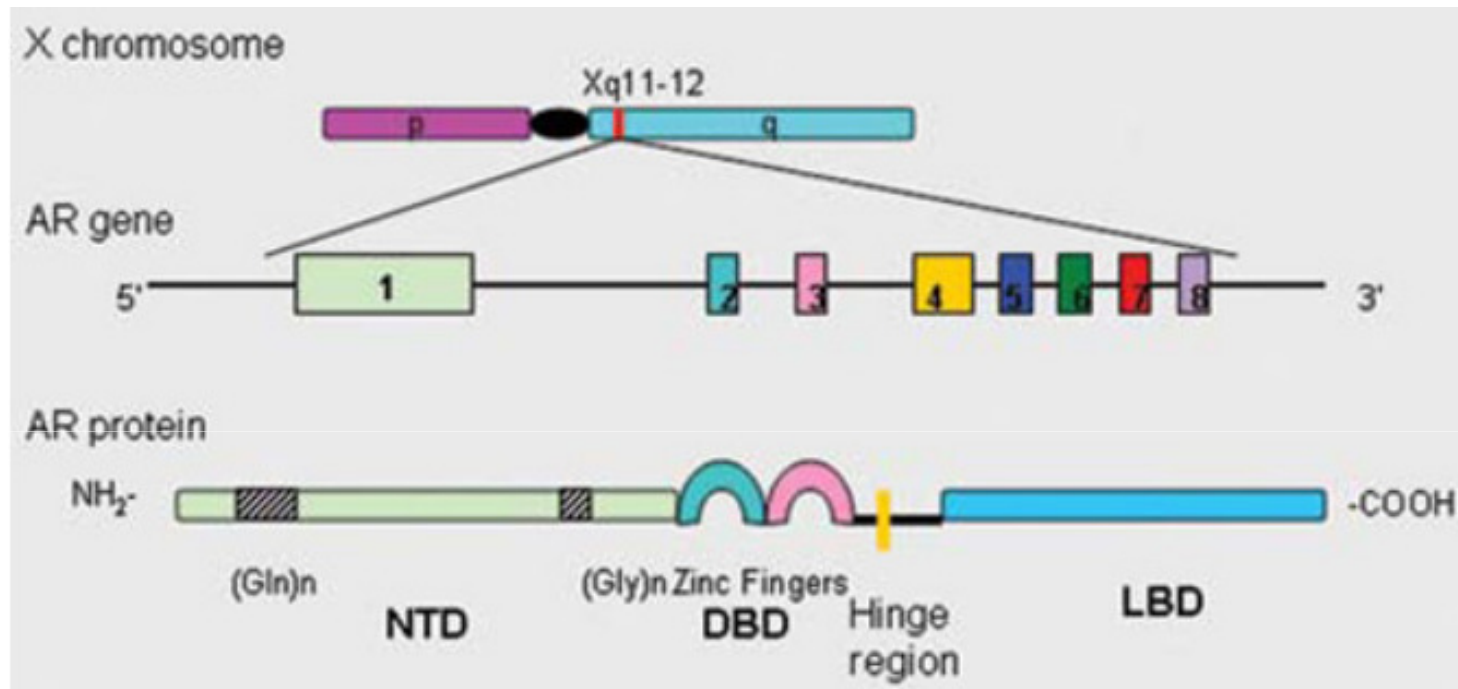
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# AR (androgen receptor) Gene



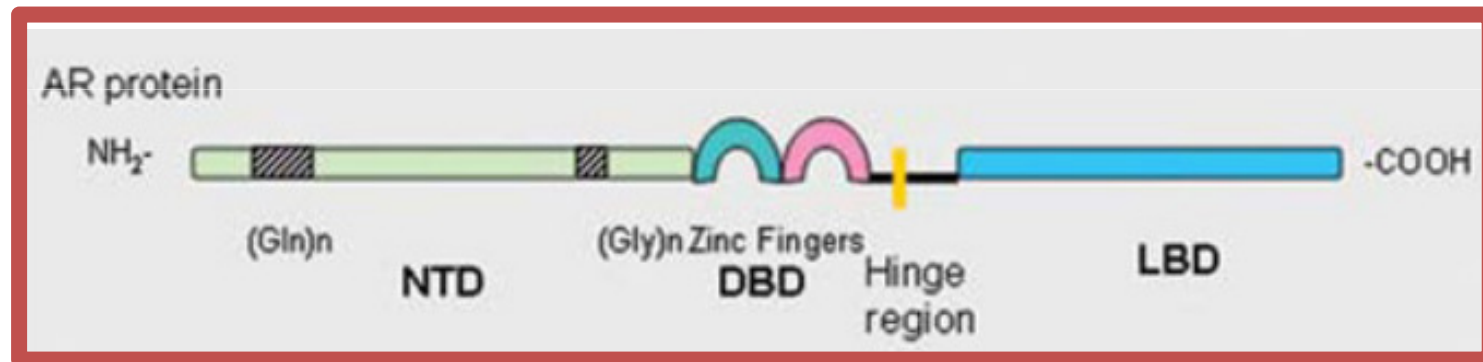
Galani A et al. Hormones 2008, 7(3):217-229

The human androgen receptor protein is encoded by 8 exons :

the NH<sub>2</sub>-terminal domain (NTD) , the DNA-binding domain (DBD), the hinge region and the ligand binding domain (LBD)



# AR Protein



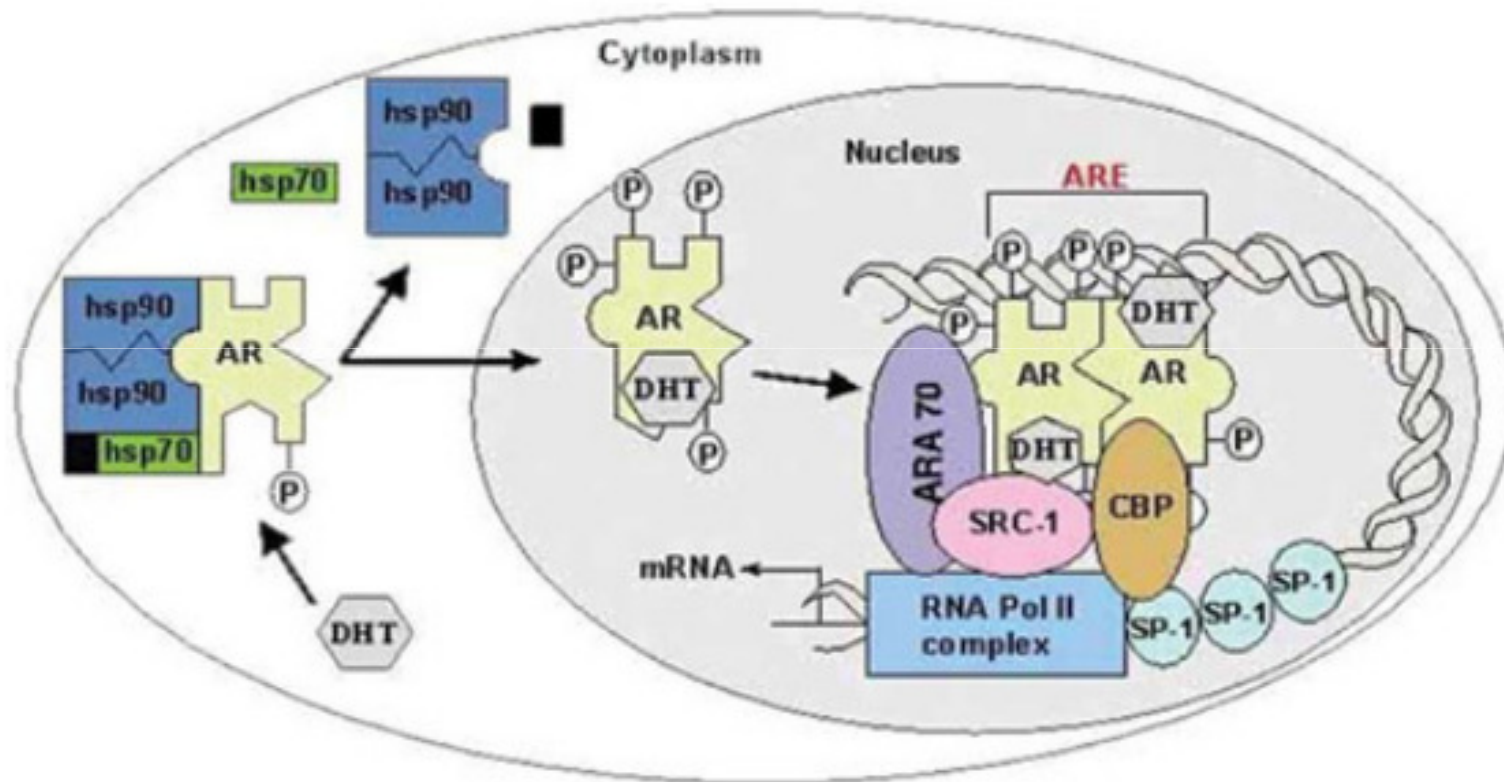
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# AR protein - sophisticated



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# AR Protein - simplified

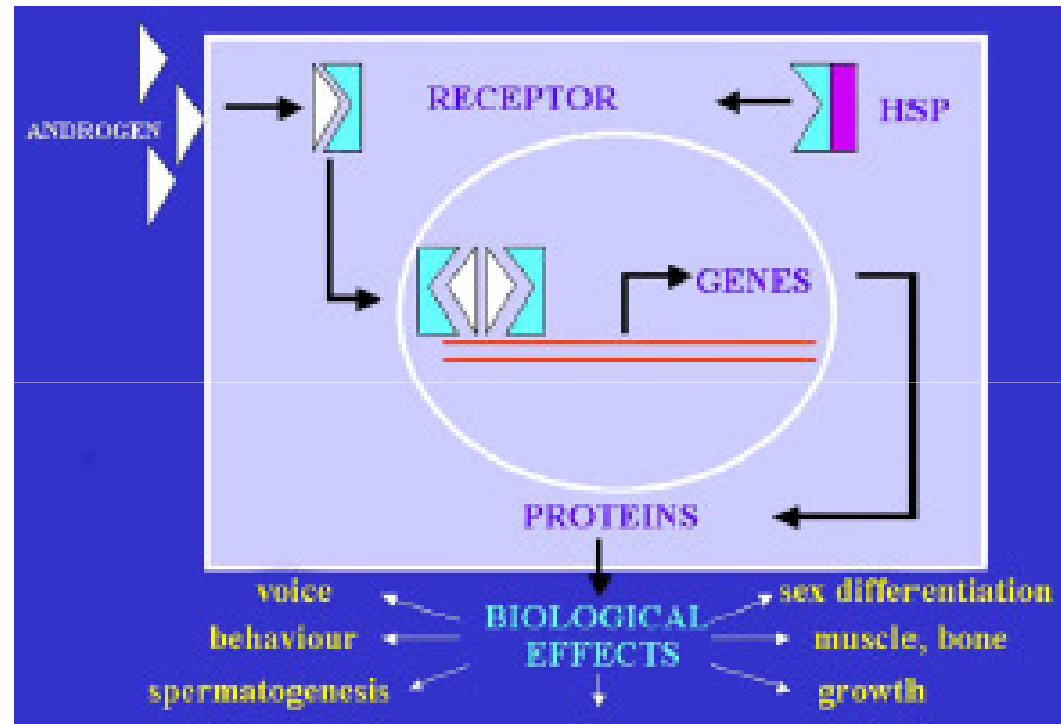


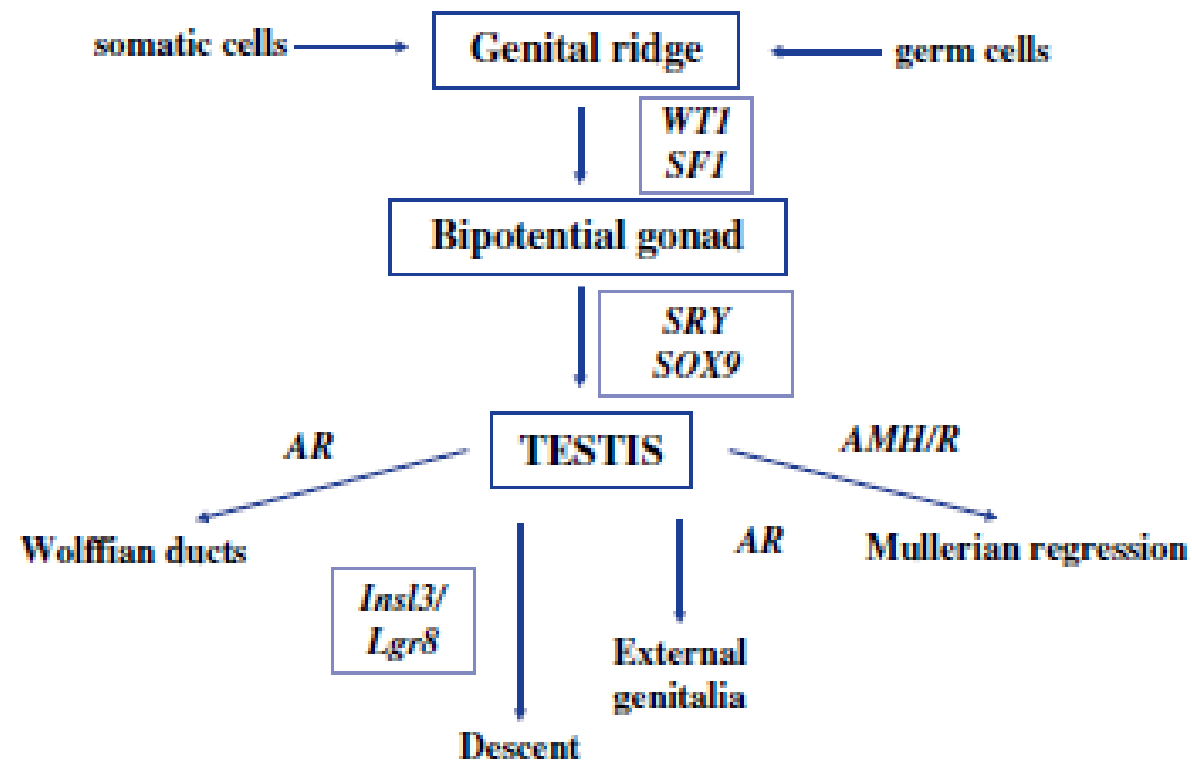
Figure 3. Schematic of androgen action and the biological effects of androgens. HSP, heat shock proteins.

Hughes IH, Deeb A. Best Practice & Research Clinical Endocrinology & Metabolism 2006;20(4):577-98



# Mechanism of disease

Pathway from testis determination to male sex differentiation with key genes indicated

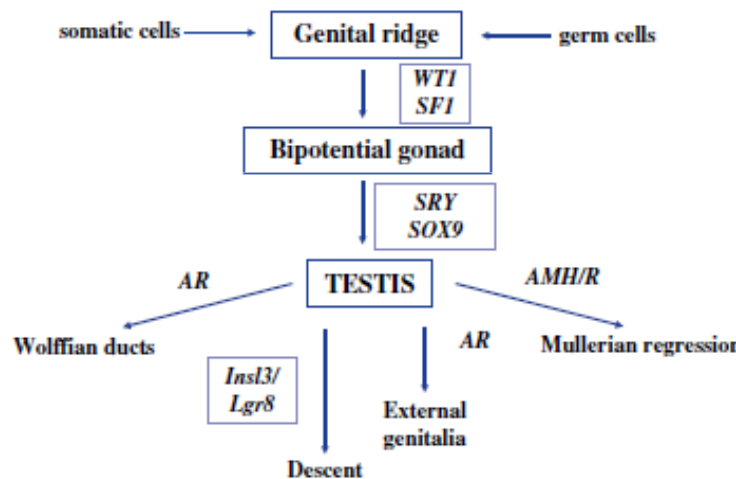


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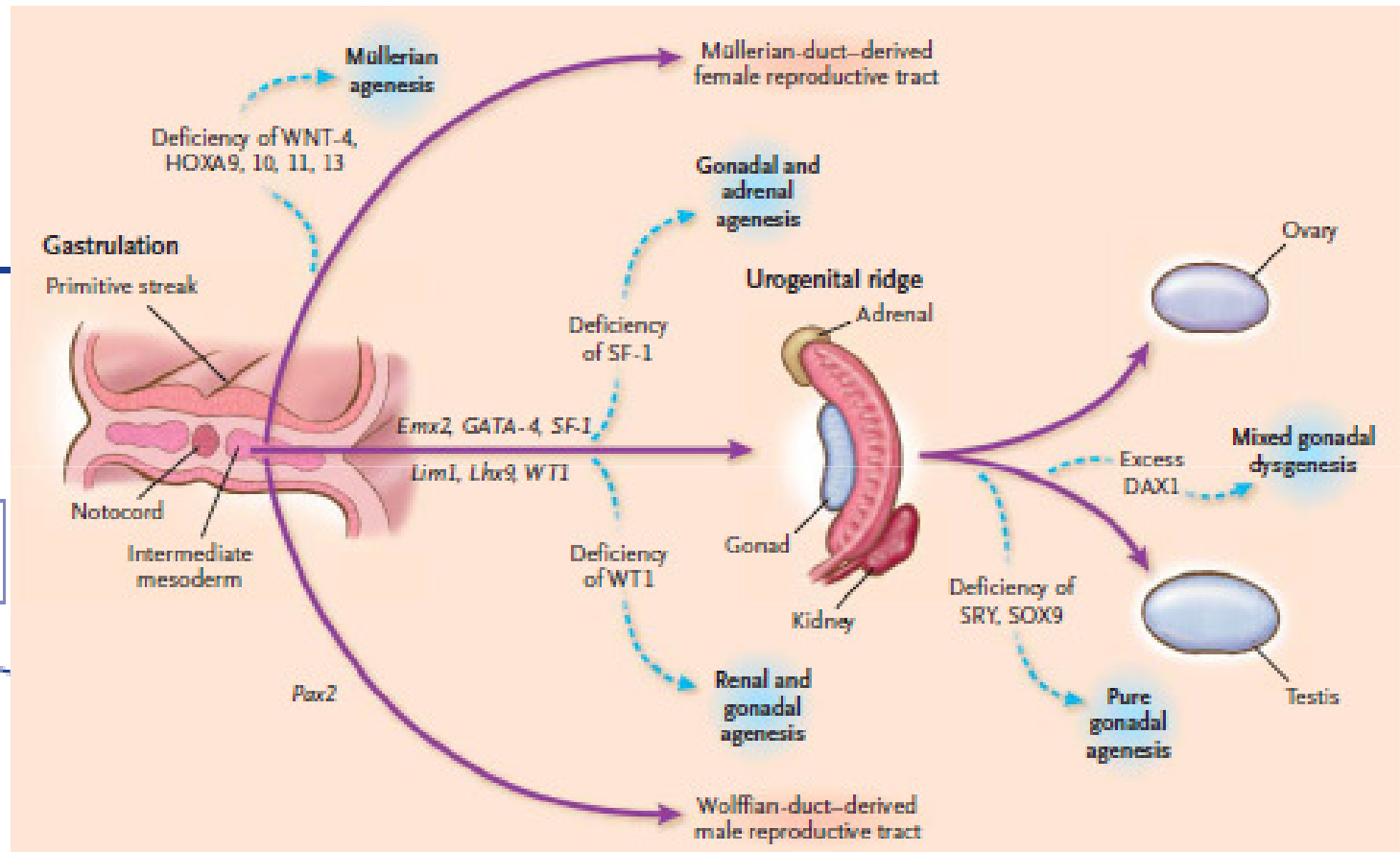
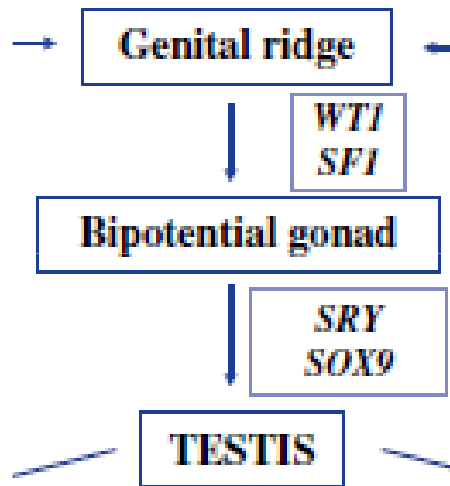
Pathway from testis determination to male sex differentiation with key genes indicated



**Table 1. Mutations in Genes Involved in Sex Determination and Development and Associated with Intersex Anomalies.**

Gene (Locus)	Protein and Proposed Function	Mutant Phenotype
WT1 (11p13)	Transcription factor	Frasier syndrome, Denys-Drash syndrome with Wilms' tumor
SF-1 (9q33)	Transcription factor, nuclear receptor	Gonadal and adrenal dysgenesis
SOX9 (17q24)	High-mobility-group transcription factor	Campomelic dysplasia, male gonadal dysgenesis or XY sex reversal
DAX1 (Xp21.3)	Transcriptional regulator, nuclear-receptor protein	Gonadal dysgenesis, congenital adrenal hypoplasia
SRY (Yp11)	High-mobility-group transcription factor	Gonadal dysgenesis
MIS, or AMH, type II receptor (12q12-13)	Serine threonine kinase receptor	Persistent müllerian duct syndrome
MIS, or AMH (19p13)	Secreted protein, causes regression of fetal müllerian duct; Leydig cell inhibitor	Persistent müllerian duct syndrome
AR (Xq11-12)	Androgen receptor, a ligand transcription factor	Male pseudohermaphroditism, complete or partial androgen insensitivity syndrome
HSD17B3 (9q22)	17 $\beta$ -Hydroxysteroid dehydrogenase, 17-ketosteroid reductase 3	Male pseudohermaphroditism
SRD5A2 (5p15)	5 $\alpha$ -Reductase type 2	Male pseudohermaphroditism*
CYP17 (10q24-25)	17-Hydroxylase: 20-22 lyase	Male pseudohermaphroditism
CYP21 (6q21.3)	21-Hydroxylase	Congenital adrenal hyperplasia, female pseudohermaphroditism
HSD3B2 (1p13.1)	3 $\beta$ -Hydroxysteroid dehydrogenase type II	Congenital adrenal hyperplasia
CYP11B1 (8q24)	11 $\beta$ -Hydroxylase	Congenital adrenal hyperplasia
StAR (8p11.2)	Steroidogenic acute regulatory protein	Congenital lipid adrenal hyperplasia

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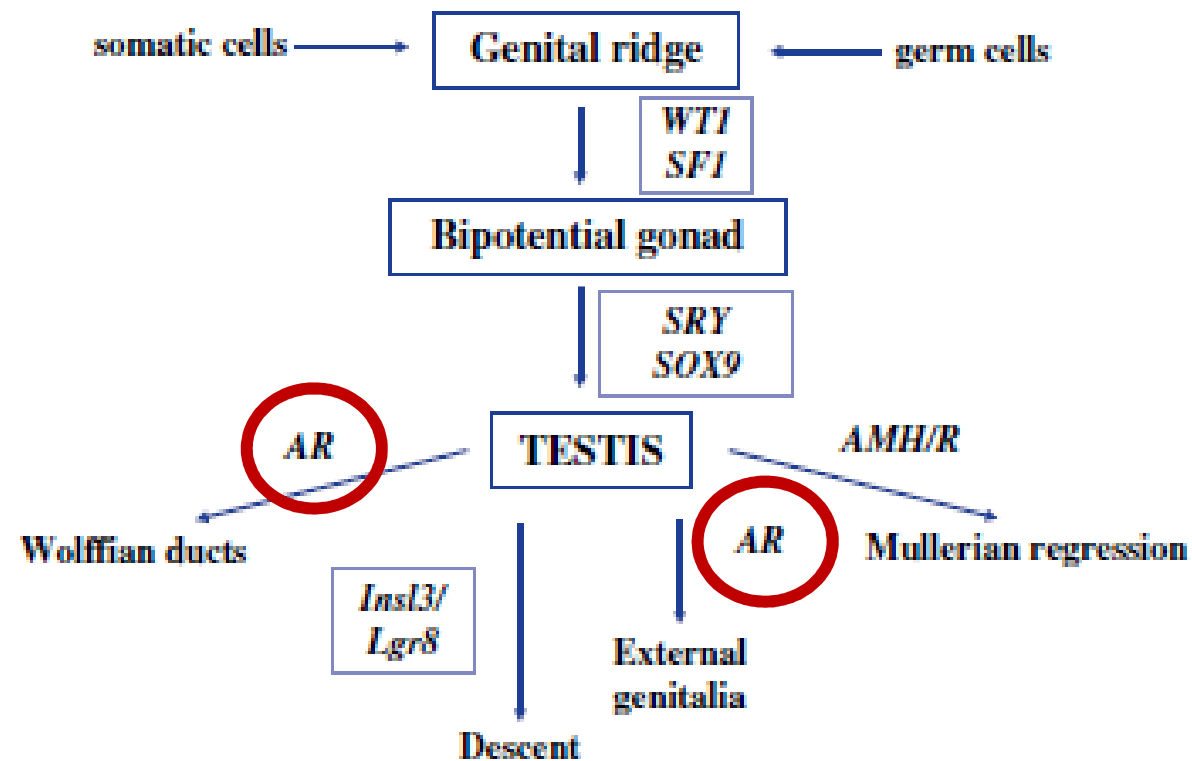


MacLaughlin DT, Donahoe PK. N Engl J Med 2004;350:367-78.

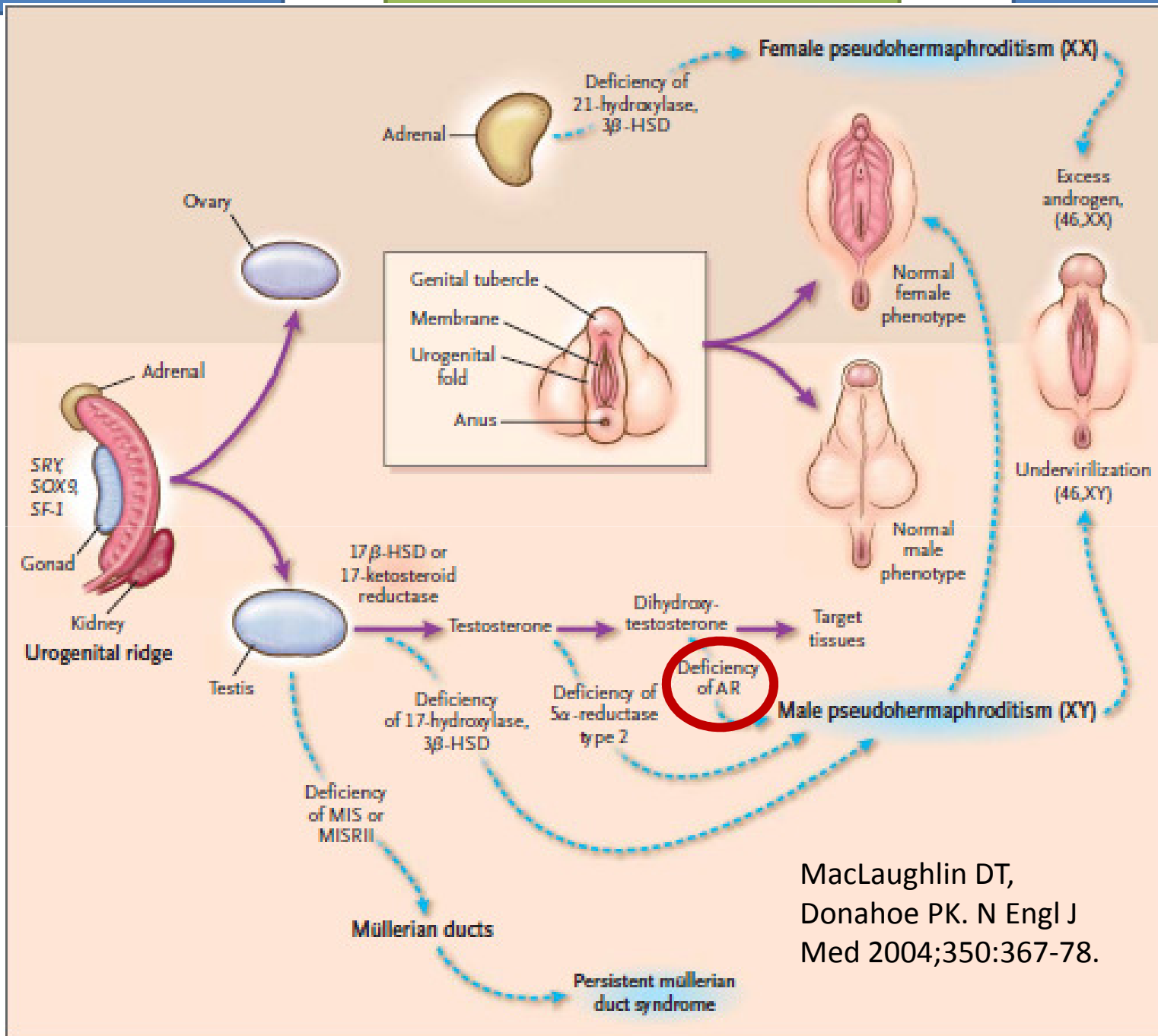


# Mechanism of disease

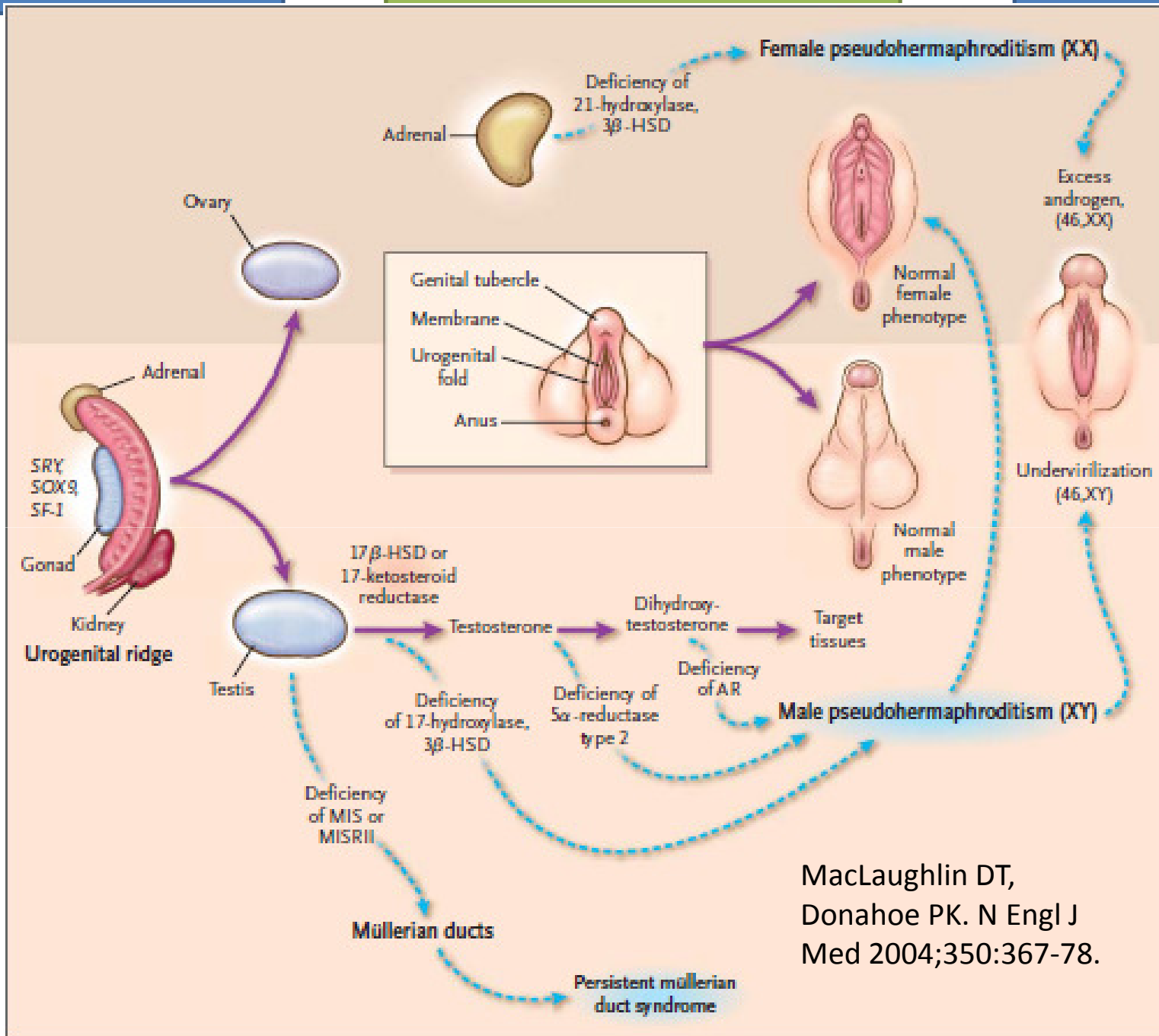
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# How to Diagnose

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# How to Diagnose

absent or defective virilization      X-linked disorder  
46,XY individuals

mutations in the AR gene.



# How to diagnose

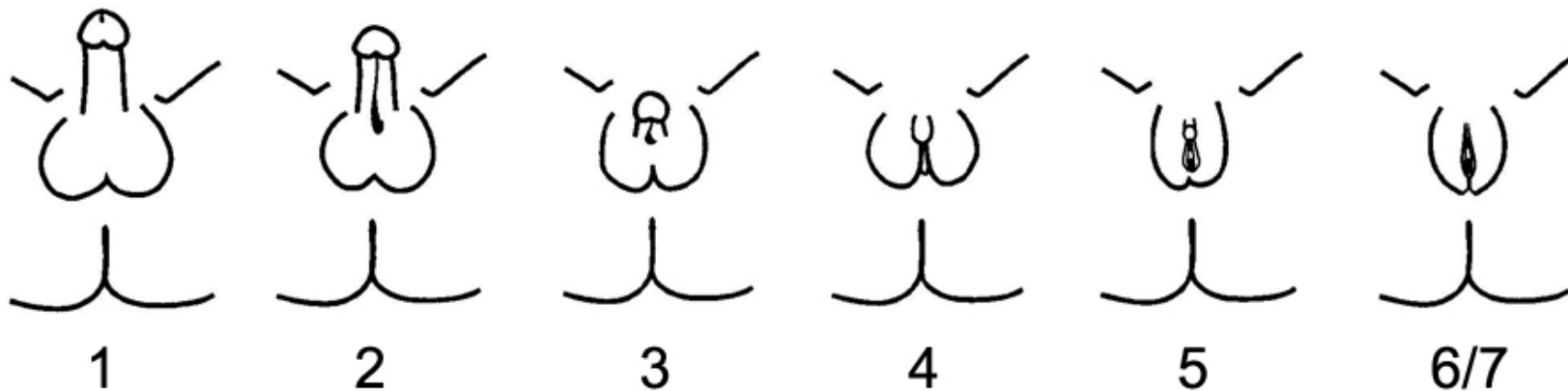
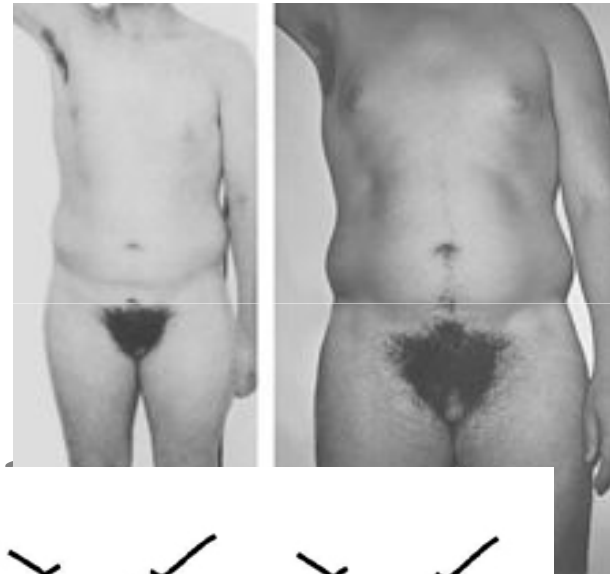
- Absent or Defective virilization
- 46,XY
- X-linked
- Mutation in the AR gene
- Other means: Hormonal examination

Pagon RA, Bird TC, Dolan CR, et al., editors. Seattle (WA): University of Washington, Seattle; 1993



# How to diagnose

- Absent or Defective virilization
- 46,XY
- X-linked
- Mutation in the AR gene
- Other reasons: Hormonal overexposure





- Absent or Defective virilization
  - Ambiguous genitalia
  - Undescended testis
  - Primary amenorrhea
  - gynaecomastia
  - Infertility

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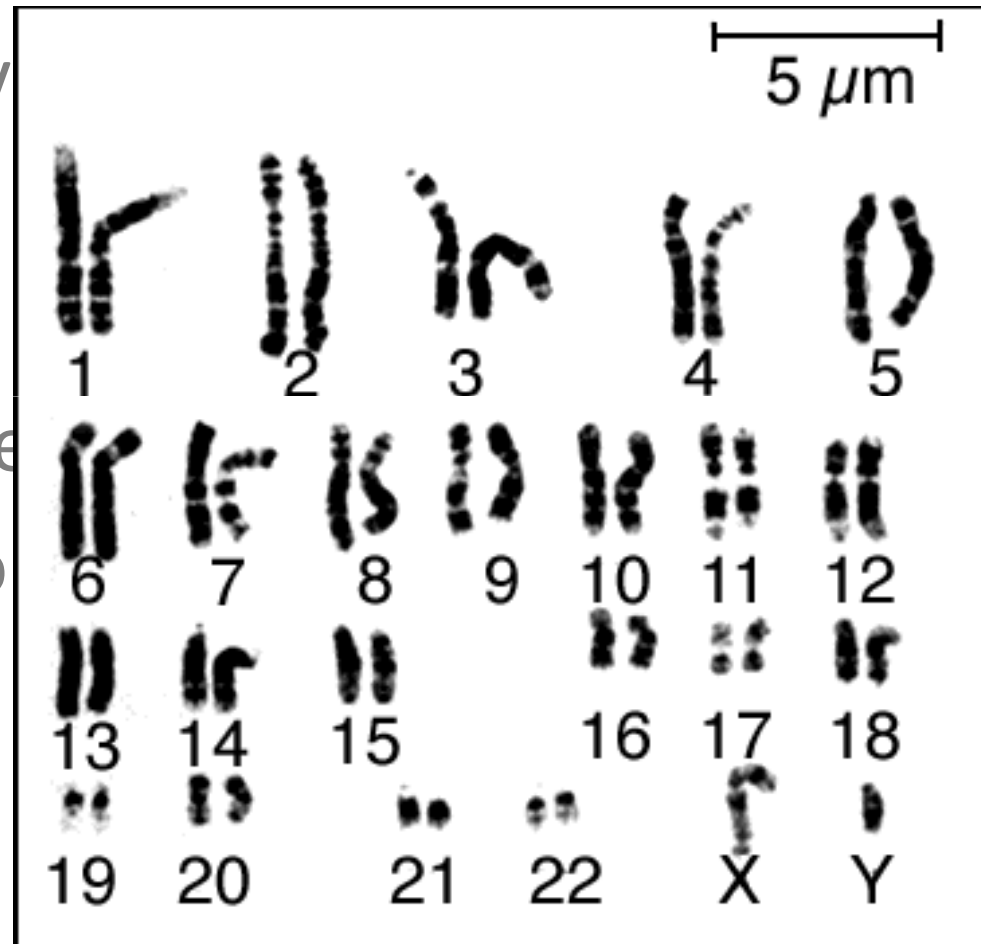
Table 1. Clinical classification of AIS phenotype according to Quigley et al, 1995.<sup>25</sup>

Type of AIS	External genitalia	Clinical characteristics
CAIS	Normal female	Female phenotype with absence of pubic or axillary hair at puberty (Grade 7).
PAIS	Predominantly female phenotype	Normal female genital phenotype; androgen-dependent pubic and/or axillary hair at puberty (Grade 6). Essentially female phenotype; separate urethral and vagina orifices; mild clitoromegaly or small degree of posterior labial fusion (Grade 5).
	Ambiguous phenotype	Severely limited masculinization; phallic structure intermediate between clitoris and penis; urogenital sinus with perineal orifice and labio-scrotal folds (Grade 4).
	Predominantly male phenotype	Predominantly male phenotype; perineal hypospadias; small penis; cryptorchidism and/or bifid scrotum (Grade 3). Mildly defective fetal masculinization; isolated hypospadias and/or micropenis (Grade 2).
MAIS	Normal male	Infertility with azoospermia; reduced virilization at puberty (Grade 1).



# How to diagnose

- Absent or Defective v
- **46,XY → karyotiping**
- X-linked
- Mutation in the AR ge
- Other means: Hormo





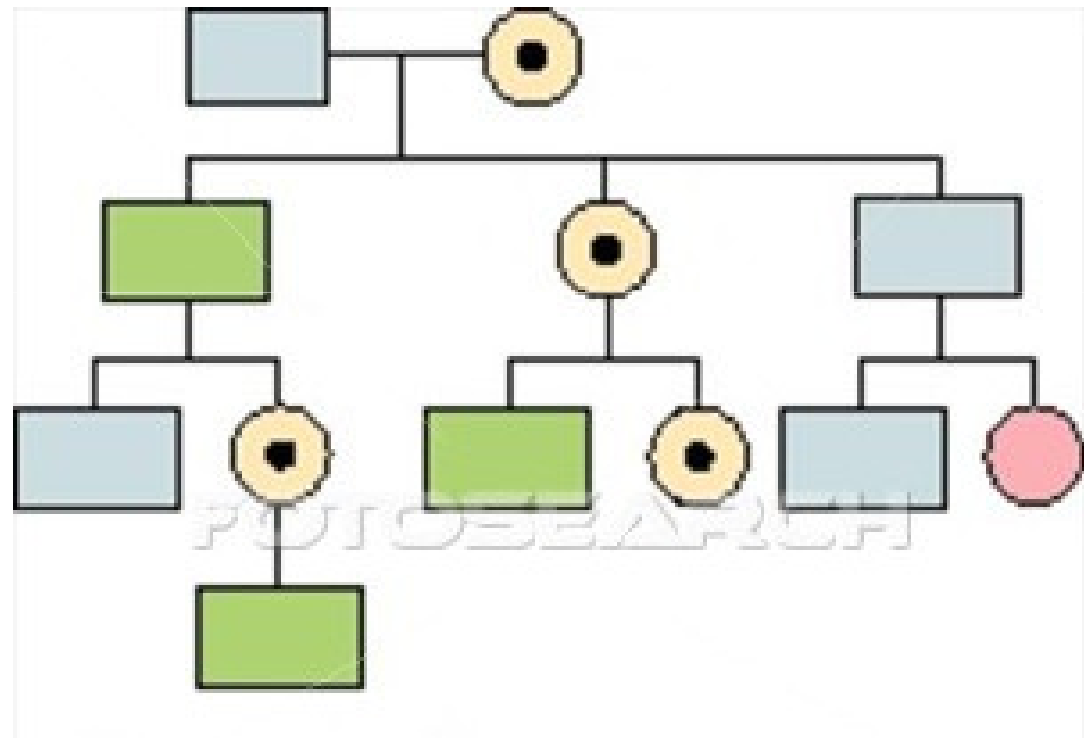
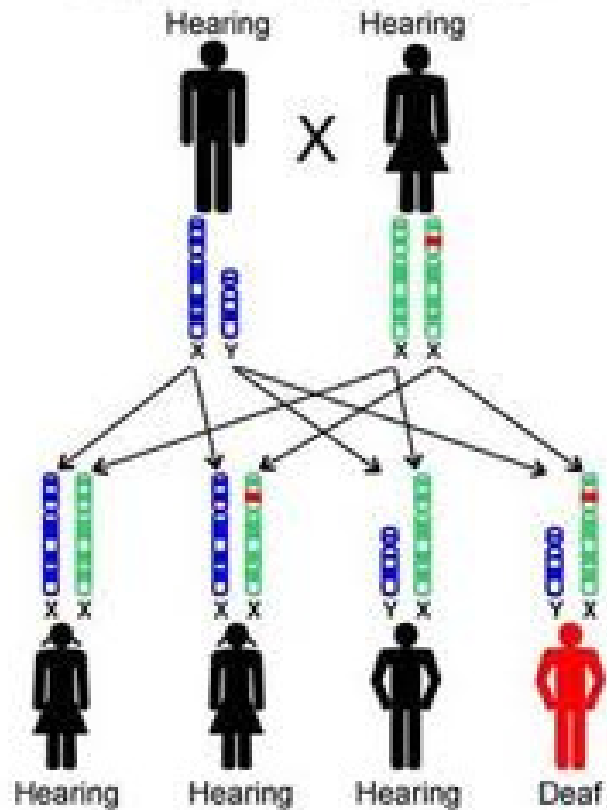
# How to diagnose

- Absent or Defective virilization
- 46,XY → karyotiping
- **X-linked**
- Mutation in the AR gene
- Other means: Hormonal examination



# X linked

## X-linked Inheritance





# How to diagnose

- Absent or Defective virilization
- 46,XY
- X-linked
- Mutation in the AR gene → molecular genetic testing
- Other means: Hormonal examination



# Molecular genetic testing

- Sequence analysis → mutation on 8 exons of AR gene → **blood of patients and mother**
  - CAIS 95%; PAIS < 50%; MAIS < PAIS



# Molecular genetic testing

- Sequence analysis → mutation on 8 exons of AR gene → blood of patients and mother
  - CAIS 95%; PAIS < 50%; MAIS < PAIS
- Deletion or duplication analysis
  - Mutation detection rate unknown
- Biopsy of genital skin → defective androgen binding



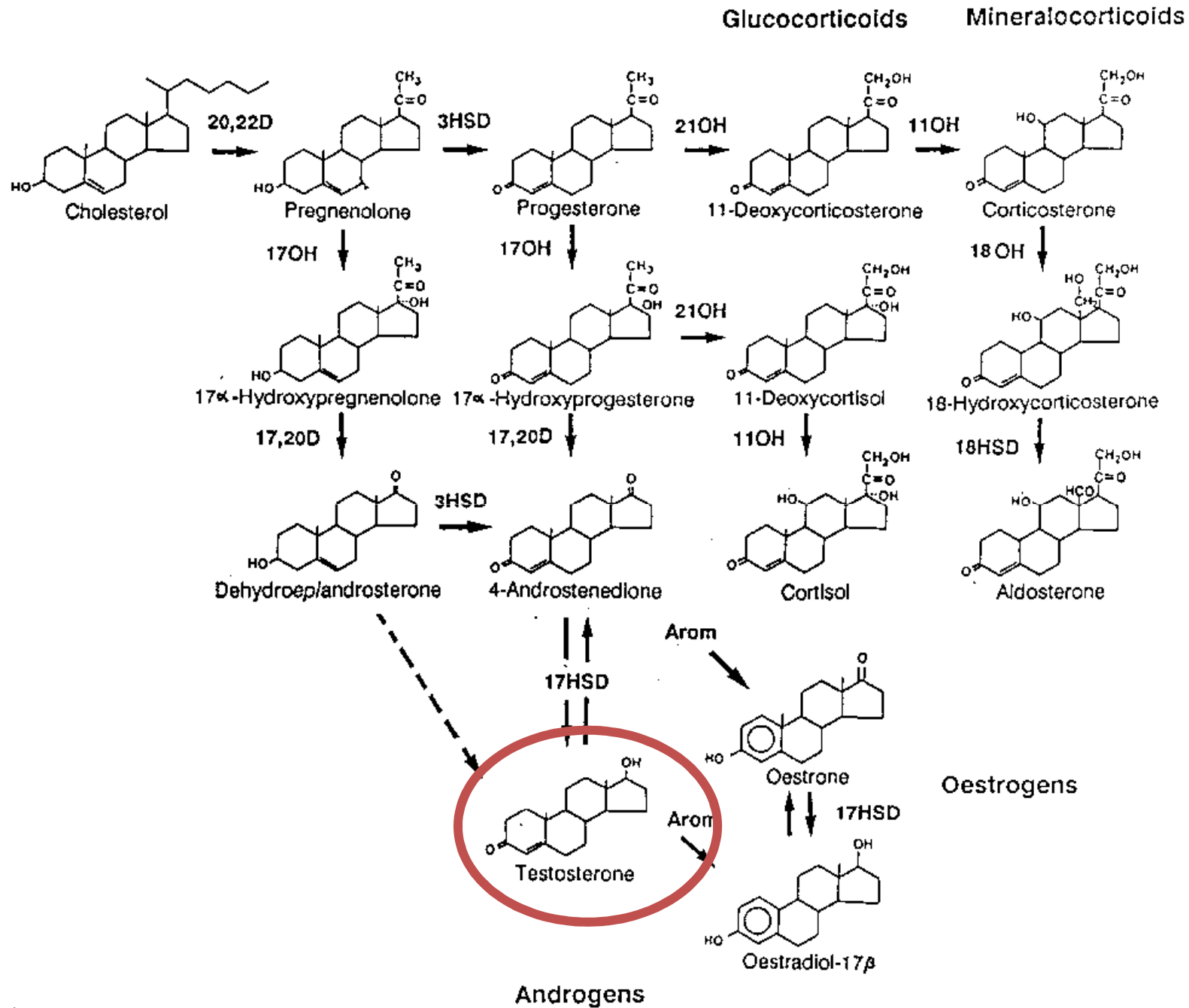
# ACMG Recommendations for Standards for Interpretation of Sequence Variations (2000).

- **Types of sequence alterations that may be detected<sup>1</sup>**
  - Pathogenic sequence alteration reported in the literature
  - Sequence alteration predicted to be pathogenic but not reported in the literature
  - Unknown sequence alteration of unpredictable clinical significance<sup>2</sup>
  - Sequence alteration predicted to be benign but not reported in the literature
  - Benign sequence alteration reported in the literature
- **Possibilities if a sequence alteration is not detected**
  - Patient does not have a mutation in the tested gene
  - Patient has a sequence alteration that cannot be detected by sequence analysis
  - Patient has a sequence alteration in a region of the gene not covered by the laboratory's test



# How to diagnose

- Absent or Defective virilization
- 46,XY
- X-linked
- Mutation in the AR gene → molecular genetic testing
- Other means: **Hormonal examination**





# Hormonal examination

- Evidence of **normal or increased** synthesis of **testosterone** (T) by the testes
- Evidence of **normal or increased luteinizing hormone** (LH) production by the pituitary gland
- Evidence of normal conversion of testosterone to dihydrotestosterone (DHT)
- Androstenedion slightly higher than normal males
- Estradiol twice the level of normal adult men
- SHBG in CAIS higher than normal females



Table 1. Short term hCG stimulation test. Protocol: 1500 units I.M. daily for 3 days.

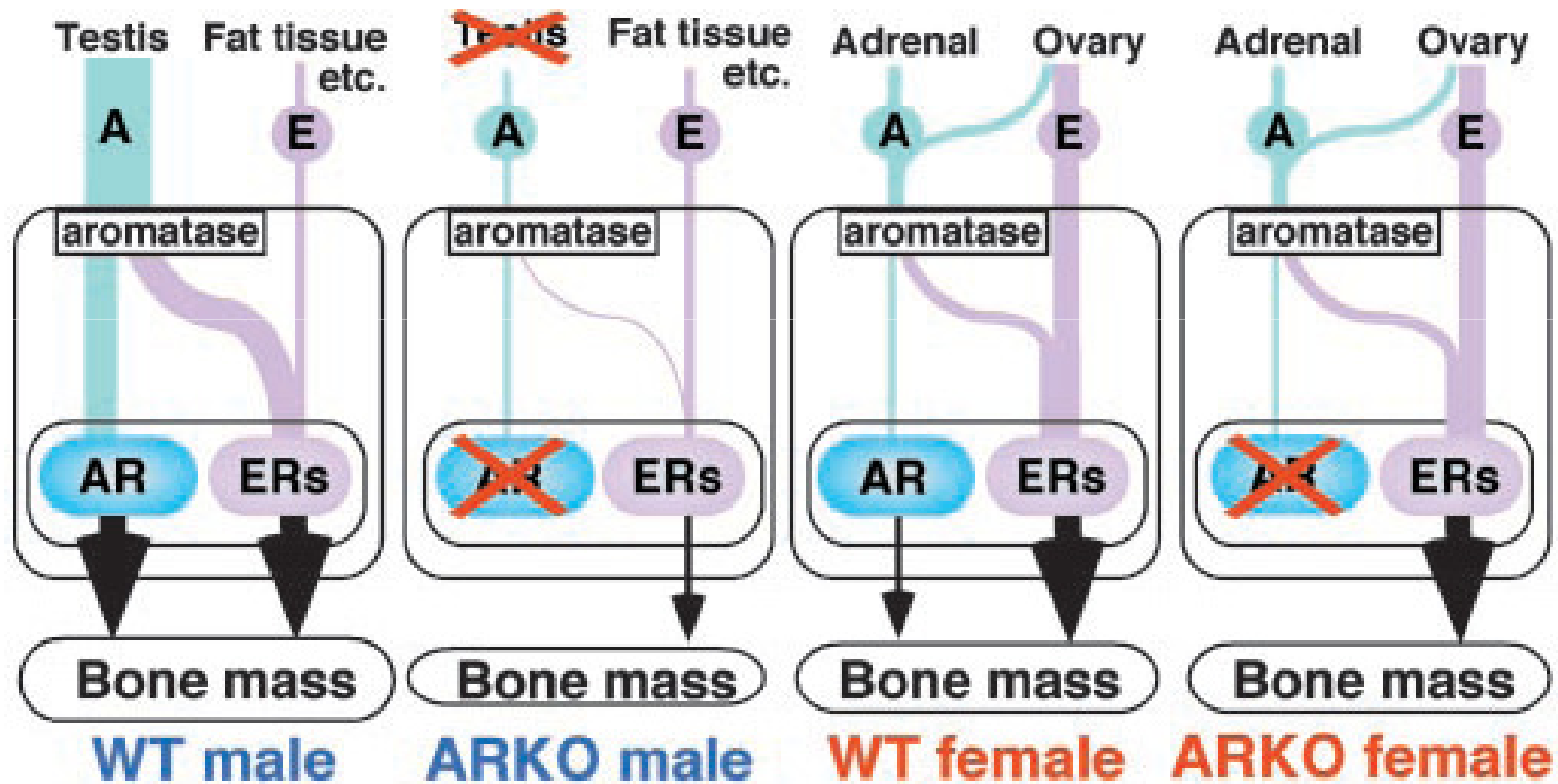
Sample time	Analytes
Baseline	LH, FSH, AMH, Inhibin androstenedione testosterone DHT
Post – hCG (24 h after last injection)	androstenedione testosterone DHT urine for steroid analysis

A longer term hCG stimulation is sometimes performed; 1500 units hCG twice weekly for 3 weeks.



# What to do?

- Gender assignment
- Surgery
  - Gonadectomy ? Gonadopexy?
  - Hypospadias or vaginal dilatation
- Genetic Counseling
  - Prepare the patient → to make decision, ready for the outcome
  - Risk assessment (De Novo 30%)
- Hormone Replacement Therapy??





# Psychology Aspect

- Male gender role behaviour in female-raised children should not be mistaken for a male gender identity
- DSD management always needs a multidisciplinary approach; a mental health professional should be part of the team
- DSD team members should avoid giving contradictory information to parents of children with DSD and older individuals with DSD
- Clinicians should timely prepare young adolescents for the consequences of their DSD for their sexual life
- Clinicians should pay specific attention to potential sexual problems in adults with DSD
- Many aspects of the clinical management of gender change that have been developed for individuals without DSD can be used for gender-dysphoric individuals with DSD

Kohen-Cettenis, PT. Best Practice & Research Clinical  
Endocrinology & Metabolism 2010;24:325–334

# Thank You Very Much

**Suggestions are expected**



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