Human gene mutations causing infertility: Genetics of hypogonadism

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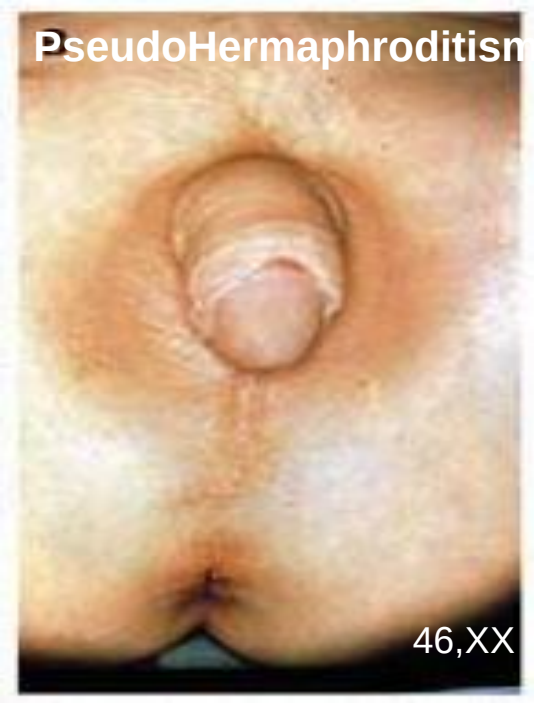
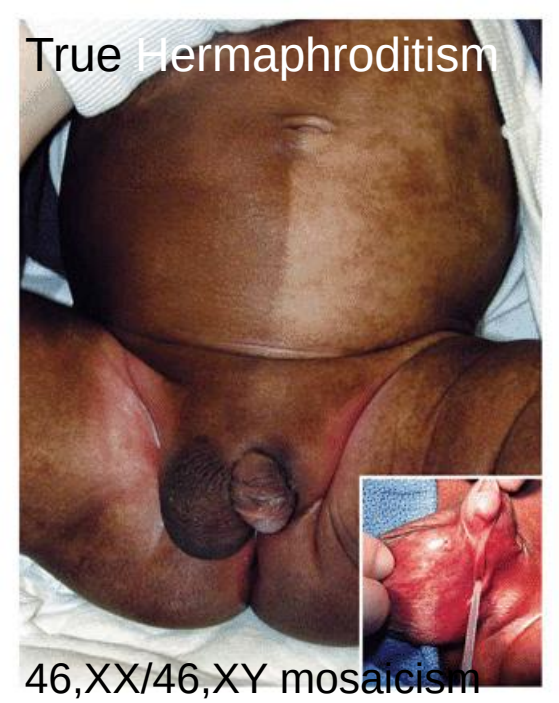
Faculty of Medicine, University of Yaoundé 2007

INTRODUCTION: overview

Gene mutation and Clinical presentation :

- Gonadal function deficiency
- Deficient puberty
- Infertility
- Abnormal genitalia



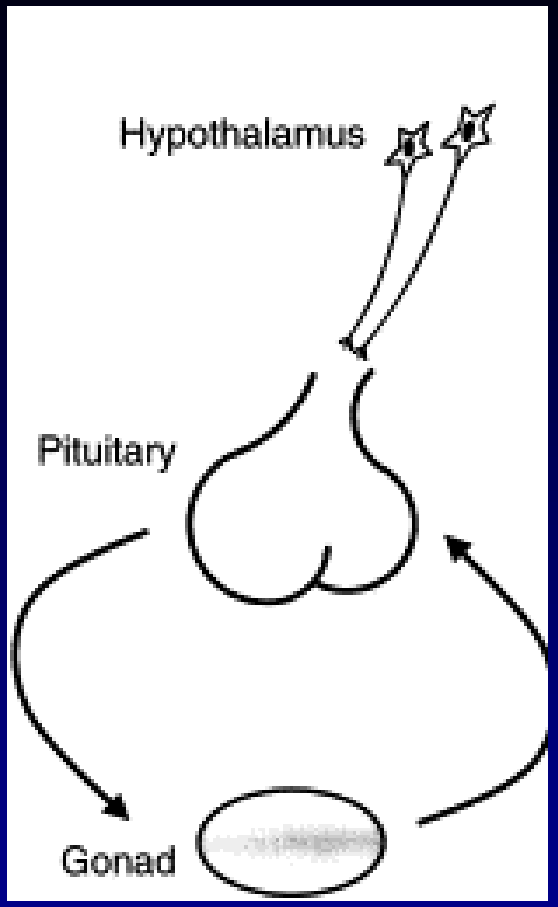


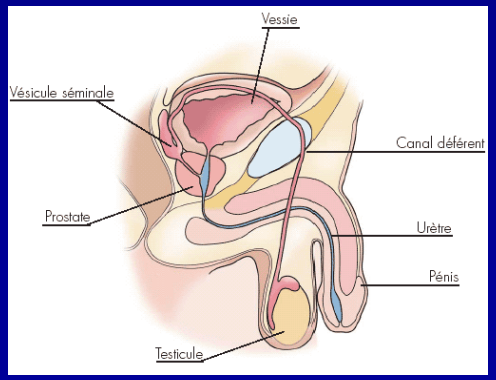
INTRODUCTION: overview

4 compartments:

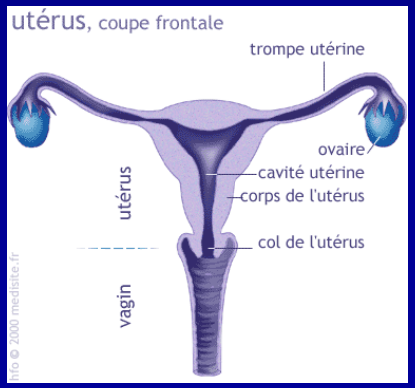
hypogonadotrophic hypogonadism: I, hypothalamic
II, pituitary

hypergonadotrophic hypogonadism : III, gonadal

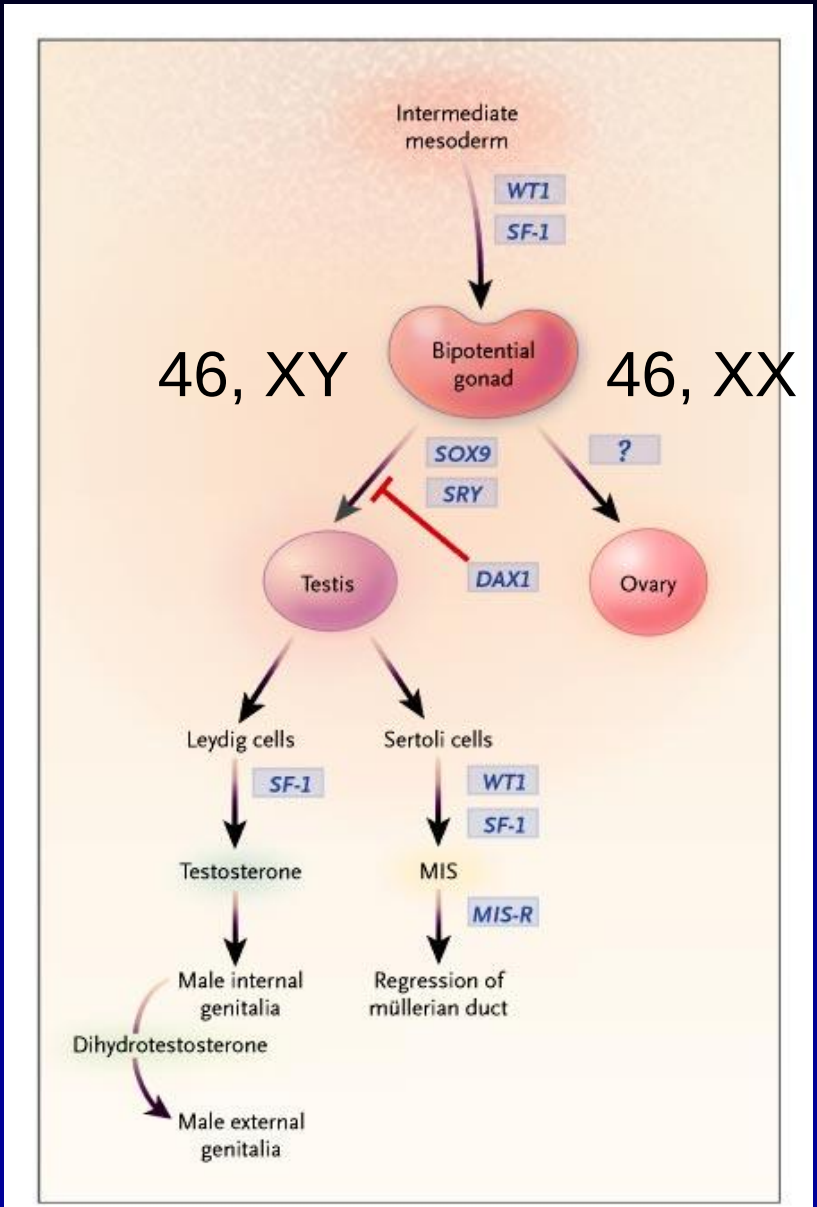




IV, outflow tract

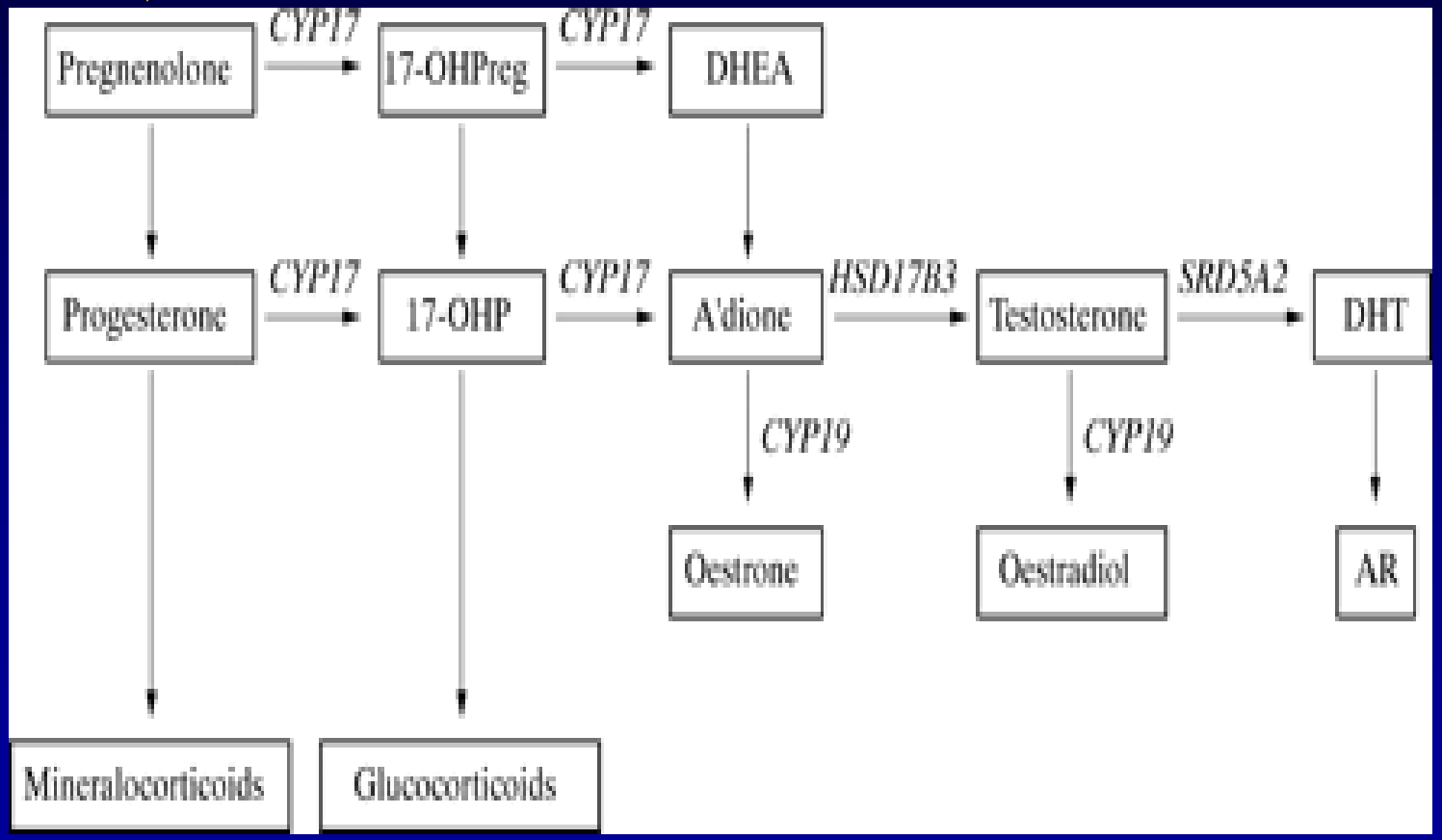


INTRODUCTION: Sexual differentiation



INTRODUCTION: the steroid pathway and gene defect

Cholesterol

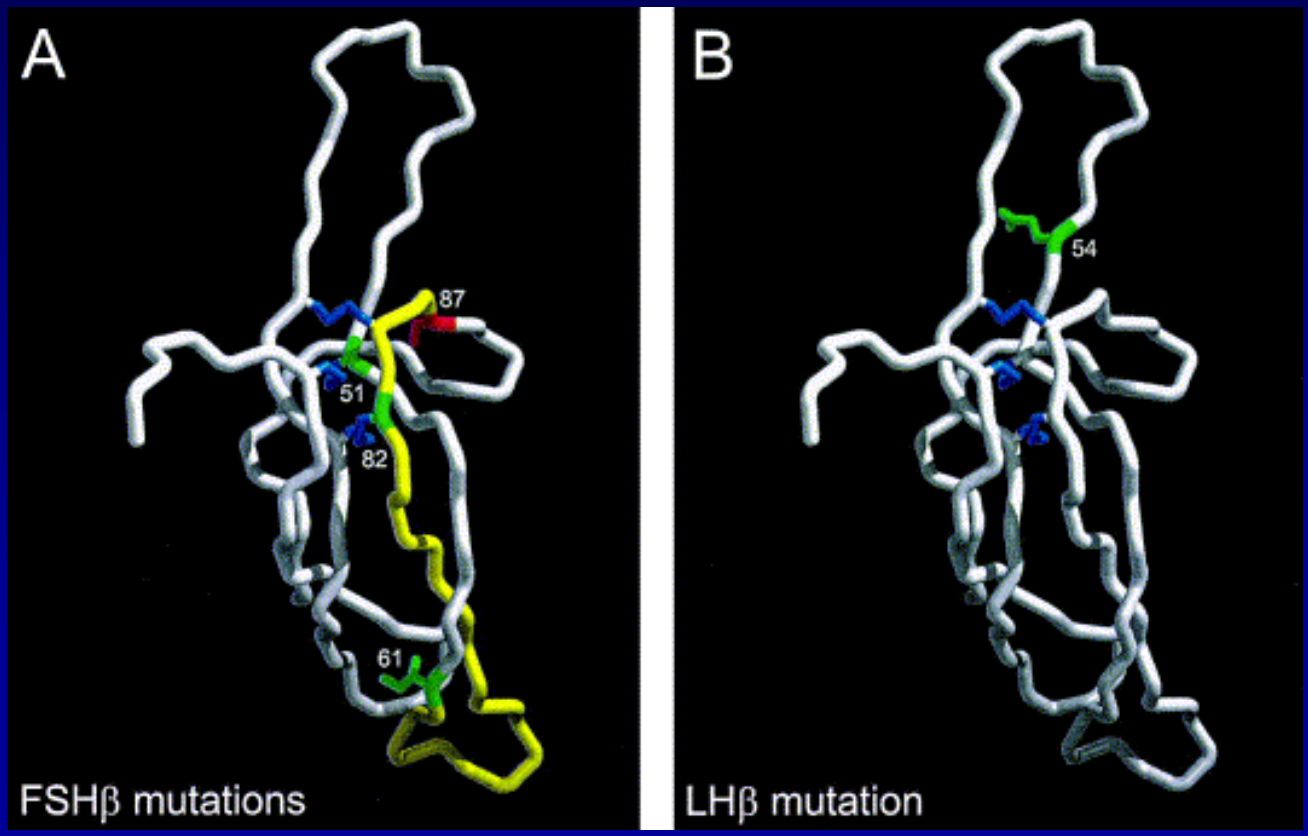


Layman LC *J Med Genet*; 2002, 39: 153-161

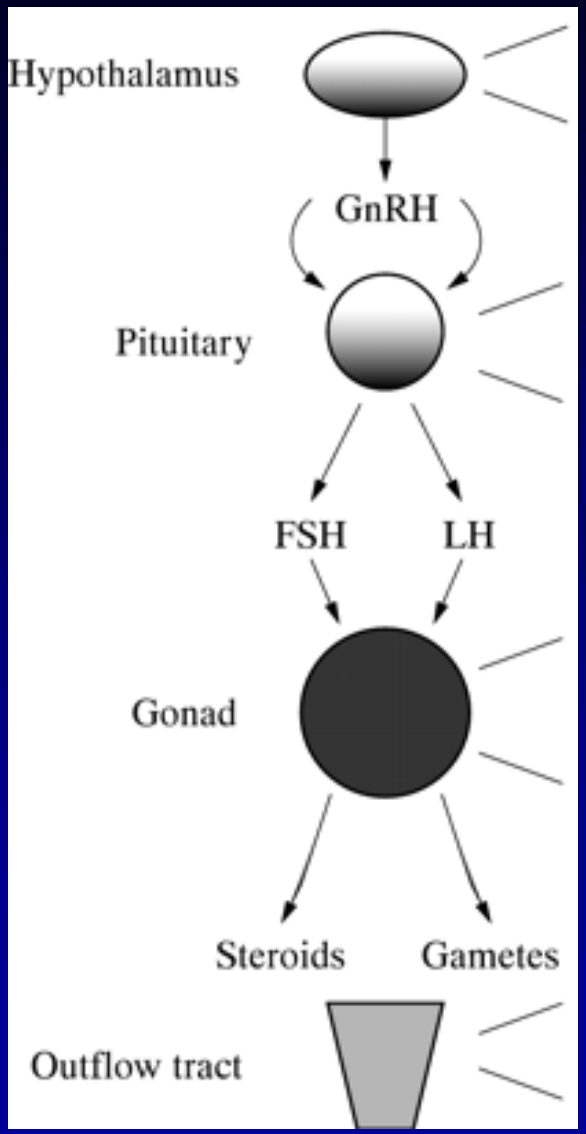
INTRODUCTION: gonadotrophic hormones

FSH, LH, hCG, TSH:

- Glycoprotein hormones
- Common α-subunits
- Specific β-subunits



INTRODUCTION: the HH-G axis gene



GPR54
KAL1
LEP
LEPR
AHC

GNRHR
FSHβ
LHβ
PROP1
HESX1
AHC

FSHR
LHCGR
GALT
AIRE
CYP19
CYP17
HSD17B3
NR5A1
SRD5A2
SOX9
WT1

45,X
delXp/Xq
FMR1
DIAPH2
POF1
FOXL2

SRY
DAZ
YRBM
USP9Y
DBY

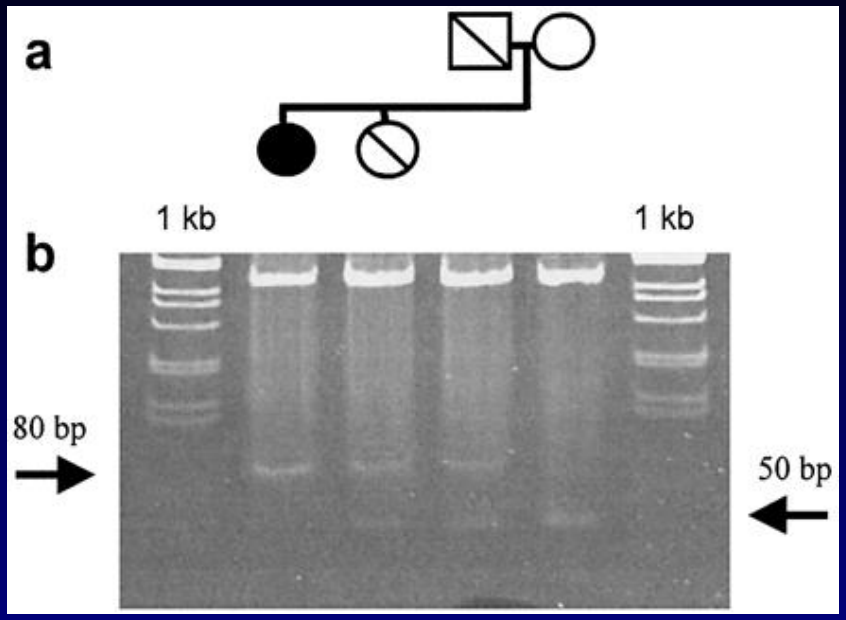
AR
CFTR
HOXA13

Layman LC. J Med Genet; 2002; 39: 153-16

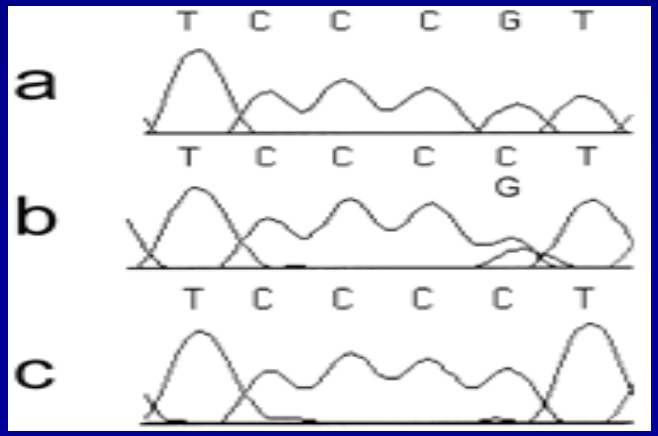
INTRODUCTION: hunting disease genes

Clinical observations
Families history, pedigree

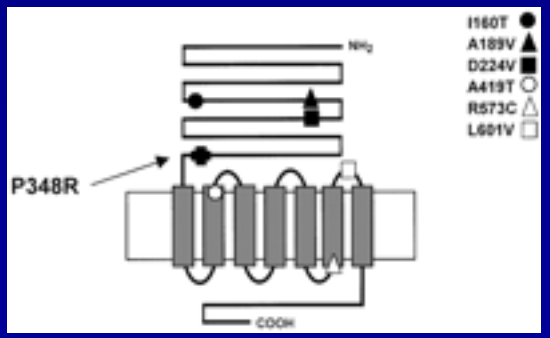
Linkage anlysis
Positional cloning



Canditate genes
Mutation identification

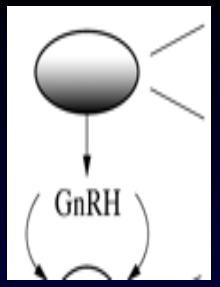


Functional studies



Allen et al. *Human reproduction*; 2003, 18, 2: 251-25

Hypogonadotrophic hypogonadism: The hypothalamic compartment



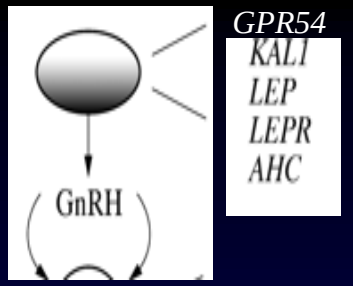
GnRH is the master

Mutations of genes expressed in the hypothalamus:

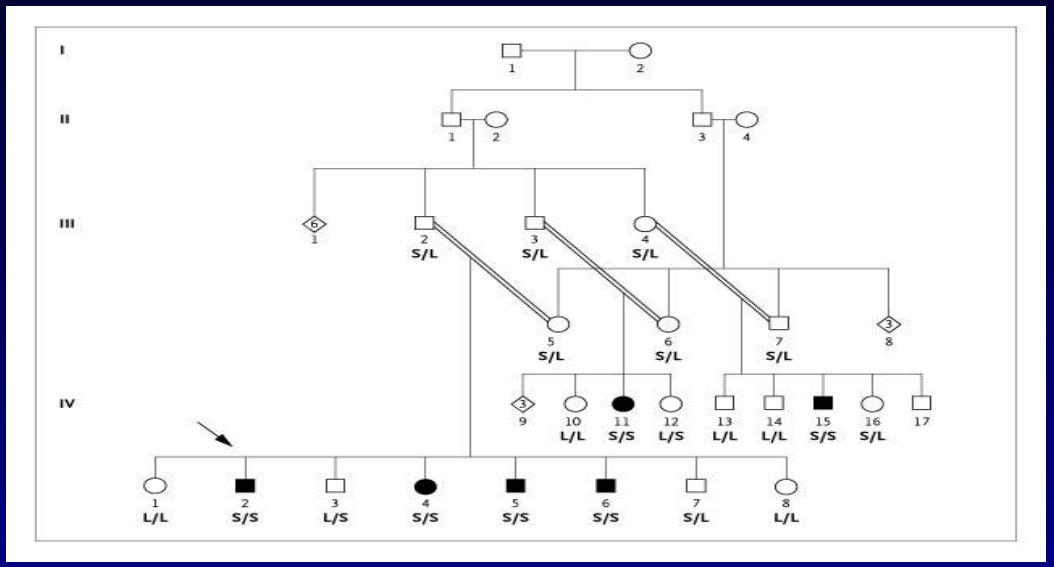
- Absent or deficient puberty
- ↓↓ FSH
- ↓ LH
- The gonads are normal

Fertility is possible: exogenous GnRH, FSH, LH

Hypogonadotrophic hypogonadism
The hypothalamic compartment
The *GPR54 gene*



- Consanguinous family



- Patients with lacked pubertal development
- Idiopathic hypogonadotropic hypogonadism (IHH)
- Candidate gene GPR54 endodes a receptor
- Affected patients : homozygous for an L148S Mutation

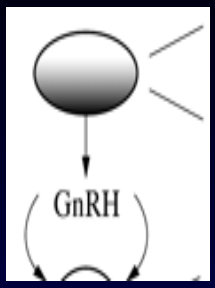
An unrelated proband: R331X and X399R mutations

Seminara et al. 2003; *N engl J Med*, 349; 17: 1614-1627

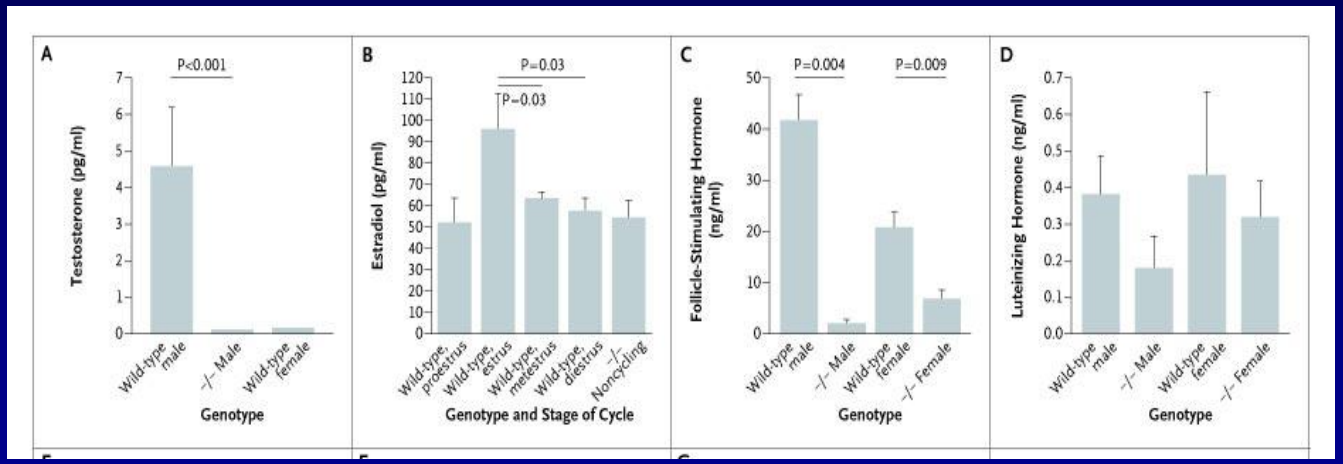
Hypogonadotrophic hypogonadism

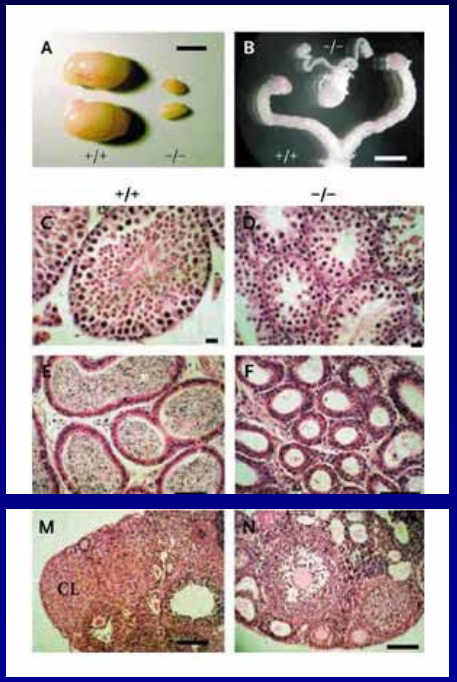
The hypothalamic compartment

The *GPR54 gene*



Gpr54-deficient mice:
Isolated hypogonadotrophic hypogonadism





- Small testis / Absence of follicular maturation
- Responsiveness to exogenous GnRH and gonadotrophin
- Normal level of GnRH in the hypothalamus

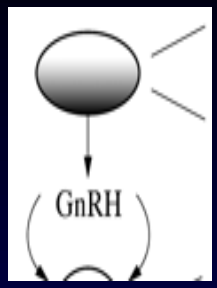
GPR54 receptor is essential for normal GnRh and puberty

Seminara et al. 2003; *N engl J Med*, 349; 17: 1614-1627

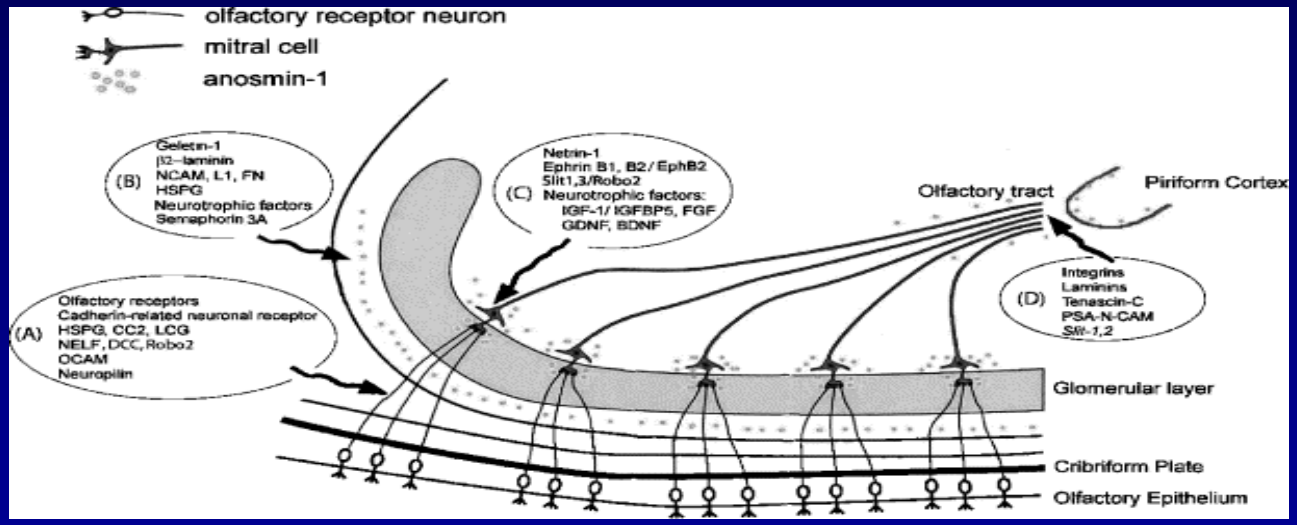
Hypogonadotrophic hypogonadism

The hypothalamic compartment

The *KAL1 gene*



- Kallmann syndrome: X linked recessive IHH + anosmia
- Mutations in the KAL1 gene (Xp)

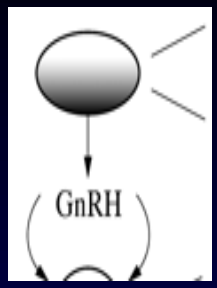


- KAL1 pt., anosmin, neural cell adhesion molecule

A scaffold for GnRH neurones and olfactory nerves to migrate

If defective : GnRH /olfactory neurones fail to synapse normally

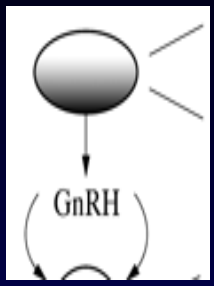
Hypogonadotrophic hypogonadism
The hypothalamic compartment
The *LEP and LEPR gene*



- The leptin deficient ob/ob mice and leptin resistant db/db mice: obesity and hypogonadotrophic hypogonadism
- Leptin mutations have been found in a human families:
  Obese subjects + hyperinsulinaemia
  Hypogonadism + irreversible pubertal delay
- A leptin receptor mutation produced a similar phenotype

Leptin plays an important role in metabolism and in puberty

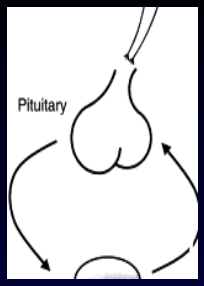
Hypogonadotrophic hypogonadism
The hypothalamic compartment,
The *ACH gene*



- Males with adrenal hypoplasia congenita (AHC) display
- Adrenal failure: ↓↓ glucocorticoids and mineralocorticoids
- AHC children fail to undergo puberty : HH ± cryptorchidism

- The AHC gene encodes pt. DAX1 (Xp): A transcription factor
- Development of the pituitary gonadotrophs and adrenal cortex
- DAX1 regulate hypothalamic and pituitary gonadotrophin

Hypogonadotrophic hypogonadism
The pituitary compartment



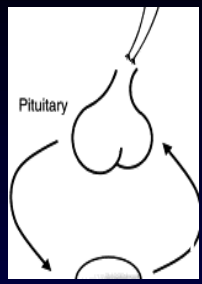
GNRHR
FSHβ
LHβ
PROP1
HESX1
AHC

- Mutations can cause deficiency in of all or some of the hormones (TSH, prolactin, Gh, FSH LH)

- Phenotype of isolated hormone deficiencies :
  - impairment of pubertal development
  - infertility

Therapy for pituitary causes of infertility is very successfull

Hypogonadotrophic hypogonadism
The pituitary compartment
The *GNRHR gene*



- GNRHR: the first AR gene to possess mutations in IHH
  Prevalence : 2.2% of all IHH

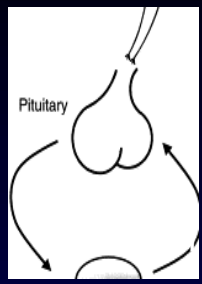
- Phenotype : complete to incomplete IHH
  no puberty / fertility or partial pubertal defects

Exogenous GnRH ↑ pituitary gonadotrophin responses

Hypogonadotrophic hypogonadism

The pituitary compartment

The *FSHβ* / LH *β* / hCG*β genes*



Female with FSHß mutations:

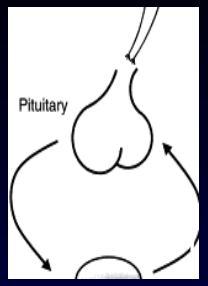
- ↓ FSH ↓ oestradiol ↑LH
- absent /incomplete breast development
- sterility

Male: Azoospermia, ↓ testosterone ± puberty

1 known homozygous missense mutation in the LHß gene

- The proband presented with pubertal delay
- Bilaterally small descended testes
- ↓ testosterone ↑ gonadotrophins
- He responded to hCG administration

Hypogonadotrophic hypogonadism
The pituitary compartment
The PROP1 gene

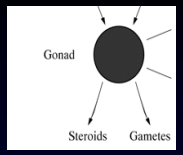


Mutations of PROP1 in humans cause combined pituitary hormone deficiency: GH, TSH, prolactin, FSH, and LH

They present with:

Short stature
Hypothyroidism
Absent puberty

Hypergonadotrophic hypogonadism
The GONAD: overview



FSHR	45,X	*SRY*
LHCGR	delXp/Xq	*DAZ*
GALT	*FMR1*	*YRBM*
AIRE	*DIAPH2*	*USP9Y*
CYP19	*POF1*	*DBY*
CYP17	*FOXL2*	
HSD17B3		
NR5A1		
SRD5A2		
SOX9		
WT1		

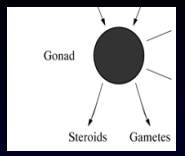
Gonadal causes of infertility constitute the largest group of disorders for which a molecular basis is known

Mutations affecting gonadal function include:

- Gonadotrophin receptors
- Steroid hormone receptors
- Steroid synthesis defects
- Miscellaneous causes

Infertility caused by gonadal failure has a poor prognosis
The best therapy involves the use of donor gametes

Hypergonadotrophic hypogonadism
The GONAD: overview



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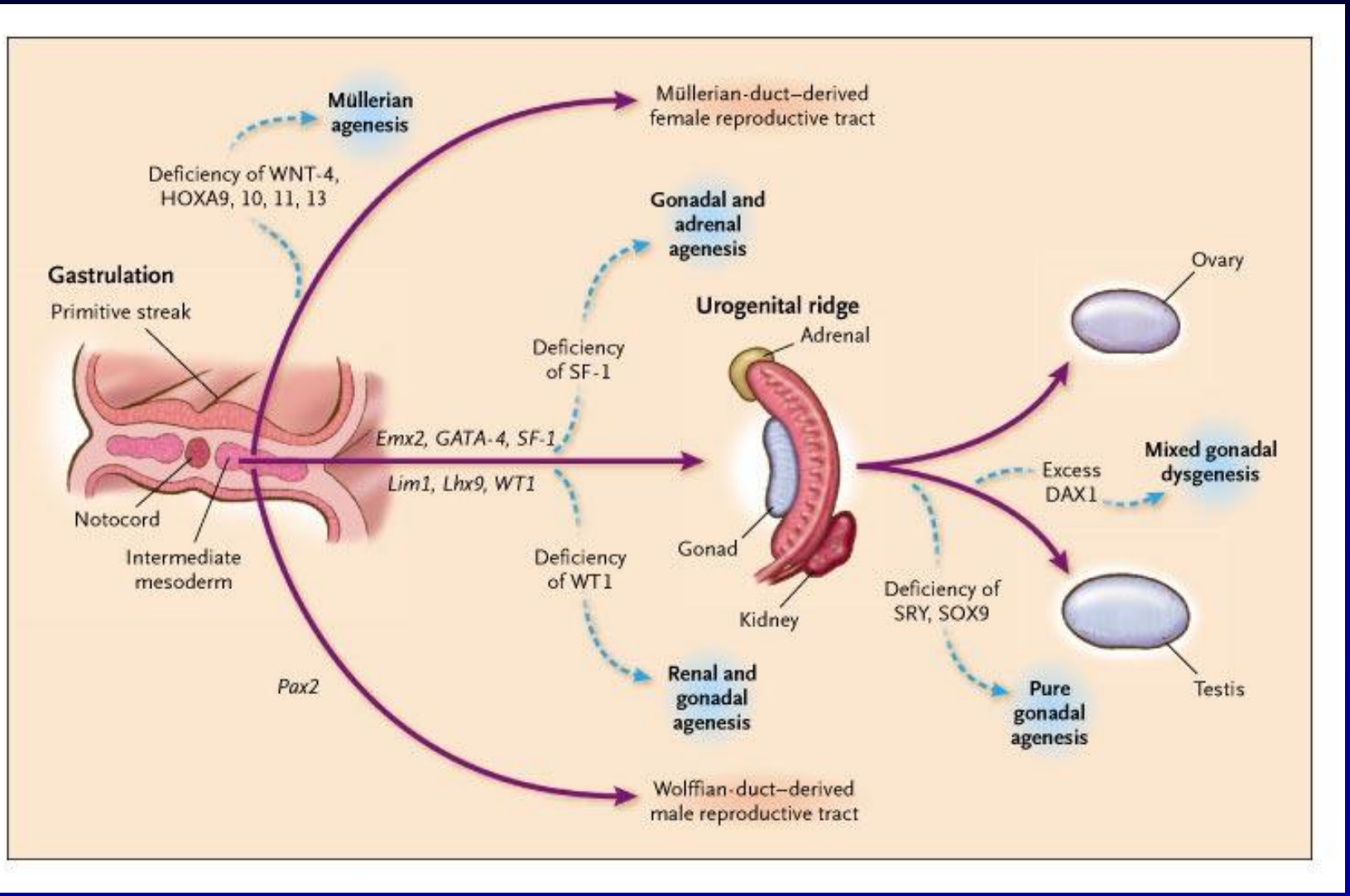
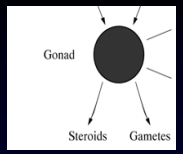


Hypergonadotrophic hypogonadism
The GONAD: X chromosome



FSHR	45,X	*SRY*
LHCGR	delXp/Xq	*DAZ*
GALT	*FMR1*	*YRBM*
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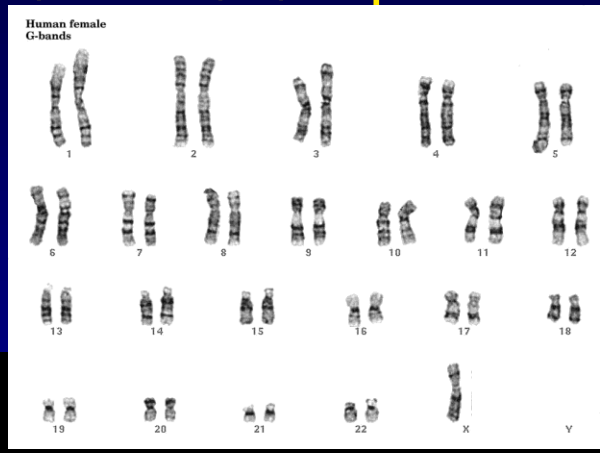
CYP17	*FOXL2*	
HSD17B3		
NR5A1		
SRD5A2		
SOX9		
WT1		

Whole X chromosome deletions: Turner syndrome, 45,X; mosaicism 46,XY, 46,XX, 47,XXX, or 46,X,iXq



- Haploinsufficiency of multiple genes
- Gonadal failure ;No puberty/menarche
- Short stature

X chromosome deletions

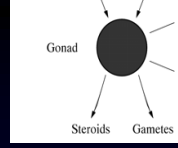
- Most women with Xp deletions are short
- Xp11 result in ovarian failure in about half of women
- Delation involving Xq generally result in ovarian failure
- POF1 region at Xq26-q28 and the POF2 region at Xq13.3-q22

X;Autosome translocations

Rare; may affect reproduction depending of the X breakpoints

Hypergonadotrophic hypogonadism

The GONAD: Single gene disorders of the X



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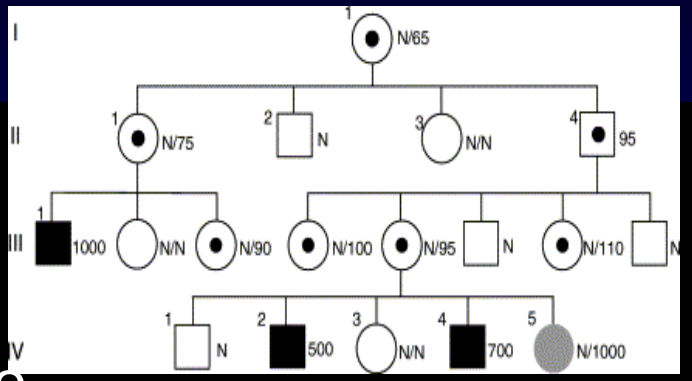


FMR1 gene

- Fragile X syndrome is an X linked AD
- Presentation: Mental deficiency in male
- The FRM1 gene (Xq27) fragile site: CGG repeat
- Premutation in carrier female

Female carriers: ↑ risk of POF

Premutation in 3% women with sporadic POF

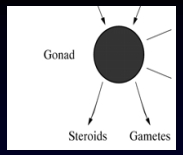
Families with POF: 12-15% FMR1 premutation alleles

Diaphanous gene (DIAPH2) :

The DIAPH2 gene in the POF2 region was disrupted in a woman with ovarian failure and balanced t(X;12)(q21;p1.3)

Hypergonadotrophic hypogonadism

The GONAD: **Y chromosome**



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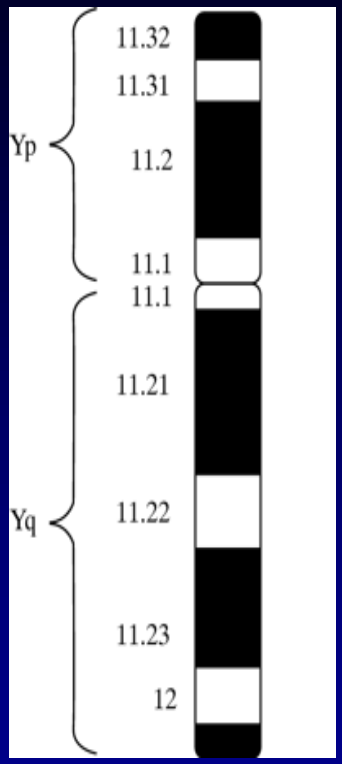


↓sperm parameters :

Oligospermia(< 20 million/cc) azoospermia (0 sperm)

Asthenospermia (< 50% motility),

Teratospermia (< 30% normal sperm)

Chromosomal disorders in men

Severe oligospermia or azoospermia:

eg: 47,XXY

46,XX men

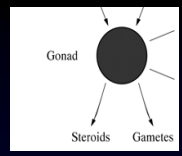
Balanced translocations (1-2% oligozoo)

SRY gene (Yp)

SRY mutations 10-15% of patients with 46,XY gonadal dysgenesis (Swyer syndrome)

Hypergonadotrophic hypogonadism

The GONAD: **Y** *Spermatogenesis genes*



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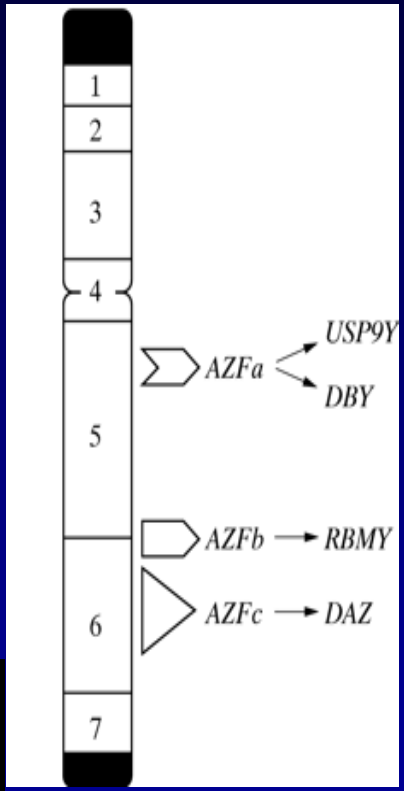
The AZF (azoospermia factor) region on Yq11

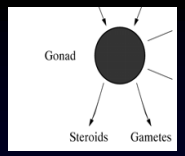
3 regions AZFa, AZFb, AZFc
spermatogenesis genes: USP9Y, DBY RBMY, DAZ



8.2% of infertile patients have deletions of one or more AZF (prevalence : 1-35%)

24% of men with azoospermia/cryptozoospermia

Hypergonadotrophic hypogonadism



The GONAD: **autosomal disorders *genes***

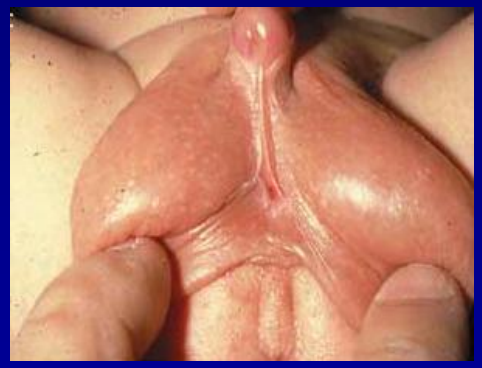
FSHR , LHCGR

Females with **FSHR gene mutations** display FSH resistance

absent or normal breast development

primary amenorrhoea or secondary amenorrhoea

The inactivating **LHCGR mutations**



46,XY: Undermasculinisation

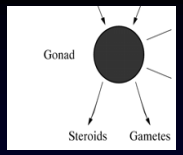
Blind ending vagina

Absent uterus and fallopian tubes

Germ cells absent

46,XX: normal sexual development and amenorrhoea

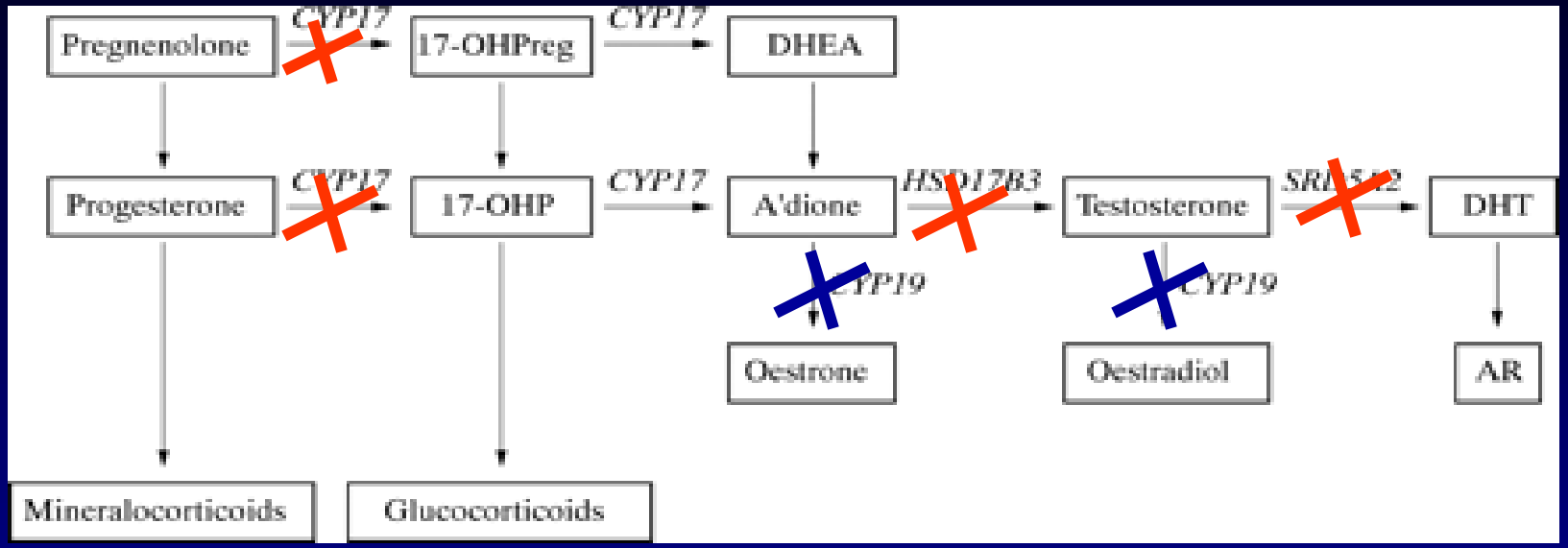
Hypergonadotrophic hypogonadism
The GONAD: *Steroid enzyme genes*



FSHR
LHCGR
GALT
AIRE
CYP19
CYP17
HSD17B3
NRSA1
SRD5A2
SOX9
WT1

45,X
delXp/Xq
FMR1
DIAPH2
POF1
FOXL2

SRY
DAZ
YRBM
USP9Y
DBY



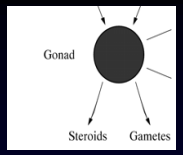
CYP17, HSD17B3, and SRD5A2 (5 α-reductase)

46,XY: female external genitalia phenotype
but not have a uterus or upper vagina

CYP19 (aromatase)

46,XX: sexual ambiguity with clitoromegaly
multicystic ovaries, no menarche

Hypergonadotrophic hypogonadism
The GONAD: *other genes*



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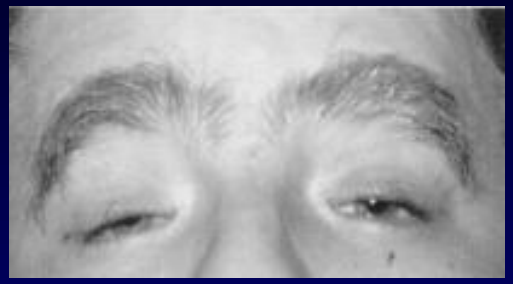


FLOX2 gene (3q23): syndrome (BPES)
Blepharophimosis-ptosis-epicanthus inversus
Affected women with type I may have POF

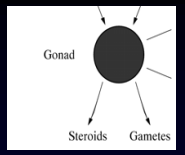
WT1 and SOX9 genes
Sexual ambiguity in 46,XY and infertility ± Wilms tumour (WT1)

Autoimmune regulatory (AIRE); gene (APECED)
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy

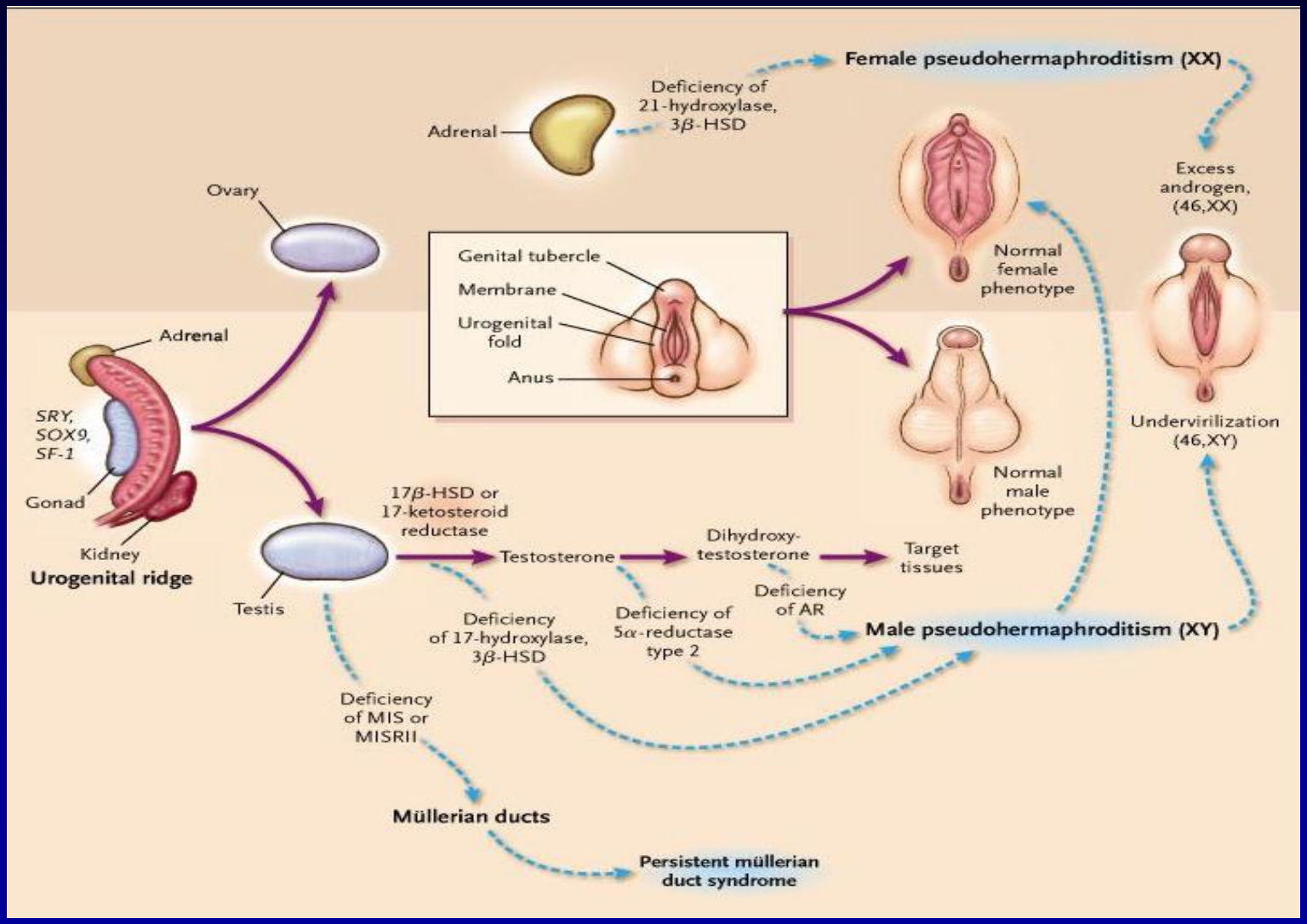
NR5A1 gene
Steroidogenic factor 1 (SF1), in the adrenal glands and gonads

GALT (galactose-1-phosphate uridyltransferase) gene
Galactose cannot be converted to glucose
Digestive and neurologic symptomatology + POF in female

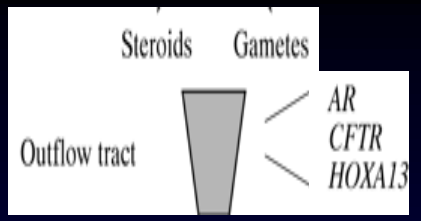
Hypergonadotrophic hypogonadism
The GONAD: overview



FSHR	45,X	*SRY*
LHCGR	del(Xp/Xq	*DAZ*
GALT	*FMR1*	*YRBM*
AIRE	*DIAPH2*	*USP9Y*
CYP19	*POF1*	*DBY*
CYP17	*FOXL2*	
HSD17B3		
NR5A1		
SRD5A2		
SOX9		
WT1		



COMPARTMENT IV: THE OUTFLOW TRACT



Androgen receptor (*AR*) gene

Nuclear hormone receptors

Mutation in 46,XY : phenotypic female + primary amenorrhoea

CFTR gene

Congenital bilateral absence of the vas deferens (CAVD):

1% of infertile males

80-90% of CAVD patients are CFTR compound heterozygotes

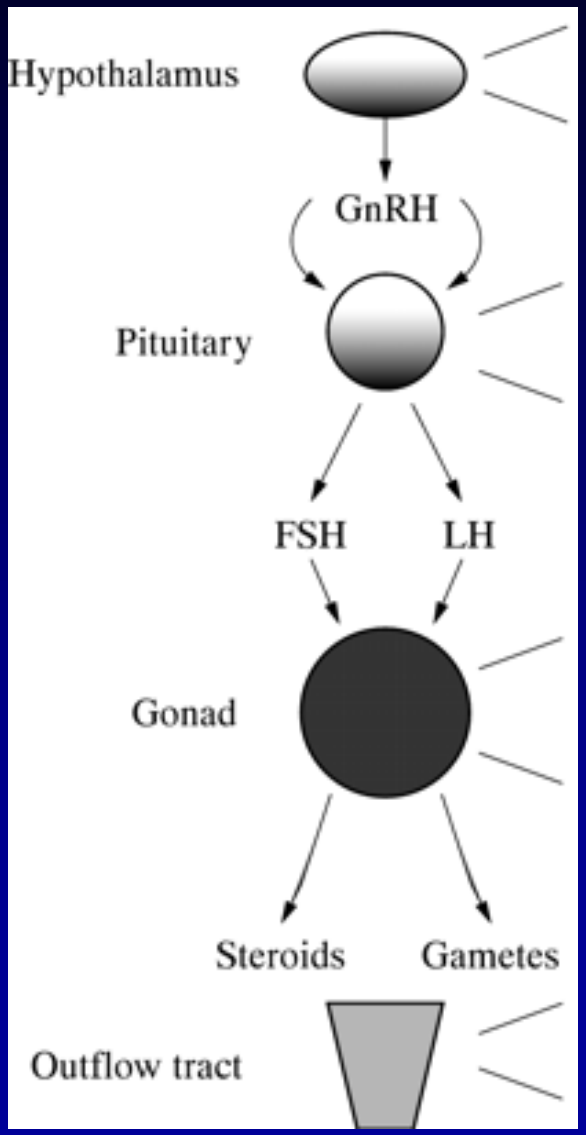
Normal testicular sperm ; ICSI /FIV

The *HOXA13* gene

Only one single gene that affect uterine development :

- Uterus: bicornuate or didelphic
- Recurrent pregnancy loss
- Hand-foot-genital syndrome

Genetics of Hypogonadism
Human gene mutations causing infertility



GPR54
KAL1
LEP
LEPR
AHC

GNRHR
FSHβ
LHβ
PROP1
HESX1
AHC

FSHR
LHCGR
GALT
AIRE
CYP19
CYP17
HSD17B3
NR5A1
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Layman LC. J Med Genet; 2002, 39: 153-161

CONCLUSIONS: genetics of hypogonadism Human gene mutations causing infertility

- Modest number of gene mutations known to cause infertility
- With the completion of the HGP, the number will increase

Ultimate goal:

- Understanding of normal reproductive physiology
- Improved infertility treatments

Genetics alone would not save Africa,
But without genetics, Africa would not be saved