Aménorrhées primitives de l'adolescente

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AES, Agadir, Maroc, 29 juin 2013

From : Le Monde (Dec. 2009)

No potential conflict of interest

Aménorrhées primitives de l'adolescente

Primary amenorrhea is a devastating diagnosis that can affect an adolescent view of her feminity, sexuality, fertility and self-image.

A prompt confirmation of the diagnosis is mandatory. When necessary, estrogen replacement treatment should be adviced for pubertal development and psychological improvement.

Primary amenorrhea in adolescence is likely to require multi-disciplinary input including that of a pediatric endocrinologist, a clinical psychologist, a pediatric surgeon and a fertility team.

Aménorrhées primitives de l'adolescente

1 - Introduction

2 - Causes of adolescent amenorrhea

3 – Announcement of diagnosis

4 – Psychological support

5 - Treatment

6 - Conclusion

Aménorrhées primitives de l'adolescente

Introduction (1)

The menstrual cycle = a biological marker of general health in adolescents

Menstrual irregularity / amenorrhea = common occurrence within the 2 years after menarche

*** Prolonged amenorrhea > 14 6/12 yrs is not normal**

↳ **Associated with significant medical morbidity**
≠ estrogen-deficient
≠ estrogen-replete

*** Amenorrhea provides a window of opportunity for early diagnosis / treatment of conditions affecting HPO axis**

Introduction (2)

Menarche and the menstrual cycle in adolescence

* The conventional wisdom about menstruation in adolescents requires updating

1. Early onset of puberty = 8-9 yrs

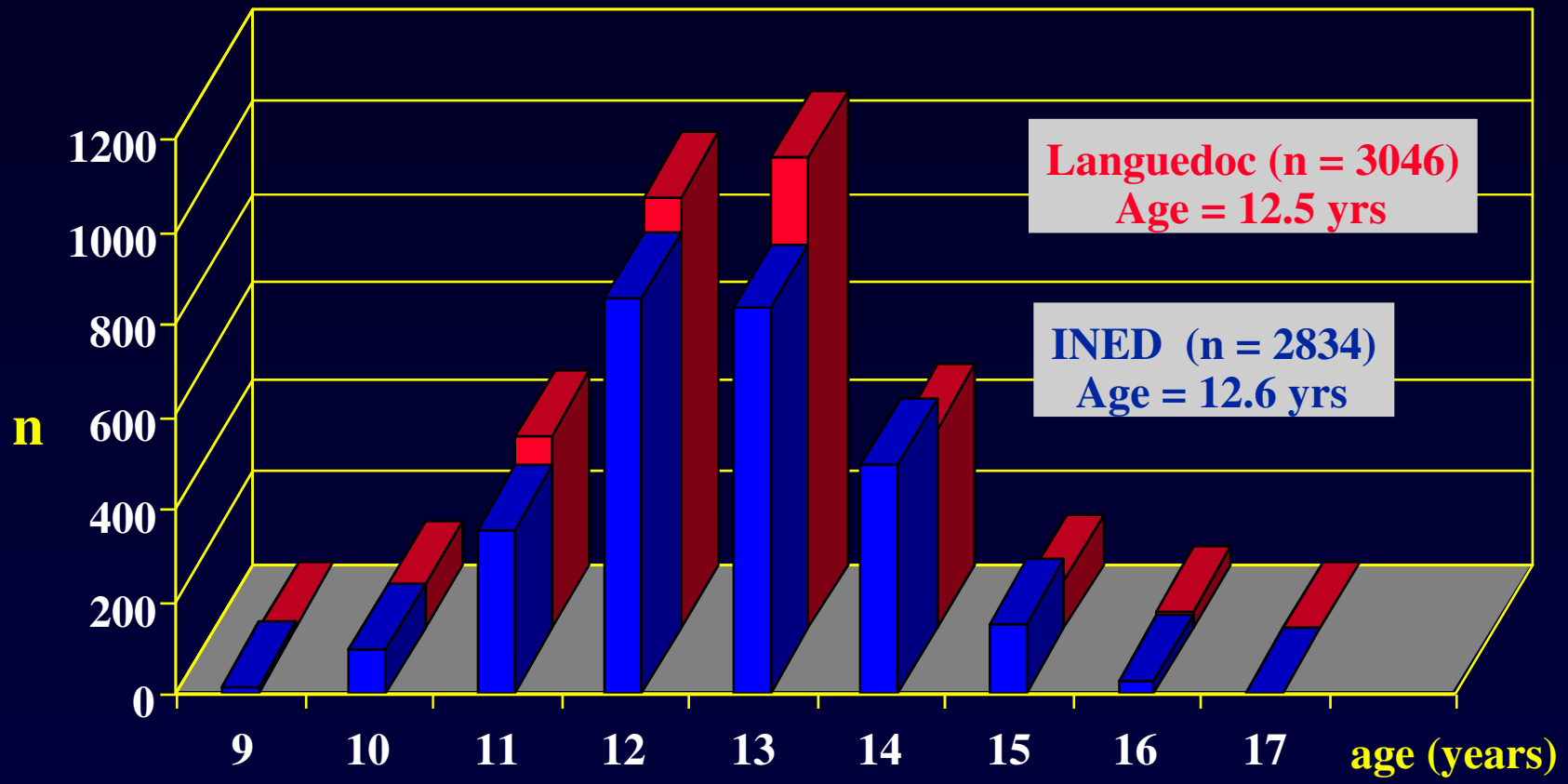
2. Age of menarche

median age = 12.5 yrs

→ 95% of adol are menstruating by 14 yrs of age

3. Racial, ethnic and social differences / age menarche

Age at menarche in France
(Epidemiological analysis = INED / Languedoc)



- median age of menarche = 12,5 +/- 0,9 yrs
- in 95% of the studied adolescents, menarche occurs < 14 ans

Introduction (3)

Why should amenorrhea be considered as a « vital » sign ?

Who should be evaluated for amenorrhea ?

How should adolescent amenorrhea be evaluated ?

What are the causes of adolescent amenorrhea ?

Aménorrhées primitives de l'adolescente

Why should amenorrhea be considered as a « vital » sign ?

1 – Early identification of potential health concerns for adulthood

2 – Early / late consequences

- **estrogen-replete adol. ⟶ hyperplasia of the endometrium**
  - **dysfunctional uterine bleeding**
  - **↑ risk endometrium cancer**
- **estrogen-deficient adol. ⟶ reduction of bone mineral density**
  - **life-long ↑ risk of fractures**

3 - Psychological problems / psychiatric disorders ?

Aménorrhées primitives de l'adolescente

Who should be evaluated for amenorrhea ?

1 – An adolescent who has not had menarche by age 15 years

2 – An adolescent who has not had menarche and more than 3 years have elapsed since thelarche

3 – An adolescent who has not had a menarche by age 13 years and no secondary sexual development

4 – An adolescent who has not had menarche by age 14 years and :

- there is a suspicion of an eating disorder or excessive exercise, or
- there are signs of hirsutism, or
- there is suspicion of genital outflow obstruction

Acc. to the Am. Acad. of Ped.

Aménorrhées primitives de l'adolescente

How should adolescent amenorrhea be evaluated ?

1 – History

- growth velocity
- pubertal development
- chemotherapy, irradiation ?

2- Physical examination

- B ?
- height and weight
- symptoms of androgen excess
- galactorrhea
- disorders of the outflow tract

3 – Lab / diagnostic tests

- FSH (LH)
- pl . testosterone
- karyotype (↑ FSH)

Acc. to the suspected origin of the dysfunction

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What are the causes of adolescent amenorrhea ?

Type	Estrogen-deficient	Estrogen-replete
Hypothlamic		
	Eating disorders	Immaturity of the HPO axis
	Exercise-induced amenorrhea	
	Medication-induced amenorrhea	
	Chronic illness	
	Stress-induced amenorrhea	
	Kallmann syndrome	
Pituitary		
	Hyperprolactinemia	
	Prolactinoma	
	Craniopharyngioma	
	Isolated gonadotropin deficiency	
Thyroid		
		Hypothyroidism
		Hyperthyroidism
Adrenal		
		Congenital adrenal hyperplasia
		Cushing syndrome
Ovarian		
		Polycystic ovary syndrome
	Gonadal dysgenesis (Turner syndrome)	
	Premature ovarian failure	
		Ovarian tumor
	Chemotherapy, irradiation	
Uterine		
		Pregnancy
		Androgen insensitivity
		Uterine adhesions (Asherman syndrome)
		Müllerian agenesis
		Cervical agenesis
Vaginal		
		Imperforate hymen
		Transverse vaginal septum
		Vaginal agenesis

NH. Golden et al,
Ann. N.Y. Acad. Sci., 2008

Aménorrhées primitives de l'adolescente

What are the causes of adolescent amenorrhea ?

Acc. to the practice committee of the Am. Soc. for Reprod. Med.

1 – Anatomic defects of the outflow tract

2 – primary hypogonadism (XX, X0, XY)

3 – Hypothalamic causes (dysfunctional, Kallman, chronic illness)

4 – Pituitary causes (prolactinoma, illness)

5 – Other endocrines gland disorders (adrenal, thyroid, ovary)

6 – Multifactorial causes (PCOS)

Aménorrhées primitives de l'adolescente

What are the causes of adolescent amenorrhea ?

Primary amenorrhea may be due to:

1 - metabolic dis. (i.e. galactosemia) obesity++

2 - autoimmune dis. (alone/auto-immune disease)

3 - infections (virus/HIV)

4 - endocrine (hypothalamo-pituitary-ovarian dis.) hypoth. Am.++

5 - iatrogenic causes (radio, chemotherapy)

6 - environmental factors (lifestyle, endocrine disruptors)

7 - genetic abnormalities

* many cases are familial

* specific genetic alterations are associated with syndromic/non syndromic forms of primary amenorrhea

8 – Mullerian defects

9 - idiopathic (60-75%)

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Review

Occupational exposures to chemicals as a possible etiology in premature ovarian failure: A critical analysis of the literature

Rémi Béranger[a,*], Pascale Hoffmann[b,c], Sophie Christin-Maitre[d,e], Vincent Bonneterre[a,f,g]

Maternal exposure to environmental disruptors/gestation

- **Methoxychlor:** early reproductive senescence
- **Bisphenol A (DES):** decreased proportion of primordial follicles
- **Benzopyrene:** decreased in primordial follicle pool

Reproductive Toxicology 33 (2012) 269–279

Aménorrhées primitives de l'adolescente

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Aménorrhées primitives de l'adolescente

What are the causes of adolescent amenorrhea ?

Genetic causes of primary amenorrhea

1 – X chromosome alterations:

- **X chromosome monosomy**
- **X deletion, translocation (POF1, POF-1B, POF-2, POF-3)**
- **BMP-15 mutation**
- **premutation of the FMR1 gene (FraX Syndrome)**

2 – autosomal genes

- **AMH/inhibin**
- **FSH-Rc**
- **GDF-9**
- **NOBOX, FOXO1A, LHX8**
- **FIGLA, POUS-F1**
- **PTEN**
- **STAR**
- **FOX-L2 +++**

NR5A1 (*SF-1*) gene variants in a group of 26 young women with XX primary ovarian insufficiency

Pascal Philibert, Pharm.D., Ph.D.,[a] Françoise Paris, M.D., Ph.D.,[a,b] Besma Lakhal, Ph.D.,[c]
Françoise Audran, Pharm.D.,[a] Laura Gaspari, M.D.,[a,b] Ali Saâd, M.D., Ph.D.,[c]
Sophie Christin-Maître, M.D., Ph.D.,[d] Philippe Bouchard, M.D., Ph.D.,[d] and Charles Sultan, M.D., Ph.D.[b,c]

We identified

1 – a new p.Arg255Cys mutation

→ functional analysis: marked decrease in transactivation of the Cyp 11a1 and AMH promoters

2 – p.Gly146Ala variant in 46.1% (vs 10%)

Fertility and Sterility® Vol. 99, No. 2, February 2013

FoxL2 mutations

3 mutations identified in Montpellier:

- **First: Duplication c.663_692dup in BPES (Pr Sultan's patient)**
- **Second: Deletion c.936_967del in isolated amenorrhea (Dr Pienkowski's patient, Toulouse)**
- **Third: c.536C>G (p.A179G) in BPES (Dr Ten's patient, NY)**

Aménorrhées primitives de l'adolescente

What are the causes of adolescent amenorrhea ?

Primary amenorrhea / ovarian defects

1 – early decrease in the primordial follicle pool

2 – incrased or accelerated follicle atresia

3 – follicle growth blockade

Aménorrhées primitives de l'adolescente

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Molecular analysis of *WNT4* gene in four adolescent girls with mullerian duct abnormality and hyperandrogenism (atypical Mayer-Rokitansky-Küster-Hauser syndrome)

Pascal Philibert, Pharm.D., Ph.D.
Anna Biason-Lauber, M.D., Ph.D.
Iva Gueorguieva, M.D.
Chantal Stuckens, M.D.
Catherine Pienkowski, M.D., Ph.D.
Béatrice Lebon-Labich, M.D.
Françoise Paris, M.D., Ph.D.
Charles Sultan, M.D., Ph.D.

Fertility and Sterility® Vol. 95, No. 8, June 30, 2011

Aménorrhées primitives de l'adolescente

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Aménorrhées primitives de l'adolescente

What are the causes of adolescent amenorrhea ?
(Personal experience)

1 – Anatomic defects of the outflow tract = N FSH, N E2 **10%**

2 – Ovarian causes = ↑FSH ↓E2 **40%**

- Turner S.
- Pure gonadal dysgenesis (X0 or XY)
- PCOS
- Radiation / Chemotherapy

3 – Pituitary causes = ↓ FSH, ↓ E2 **5%**

- Prolactinoma

Aménorrhées primitives de l'adolescente

What are the causes of adolescent amenorrhea ?

4 – Hypothalamic causes = ↓ FSH, ↓ E2 **10%**

- Kallman

5 – Functional causes = ↓ N FSH, ↓ E2 **35%**

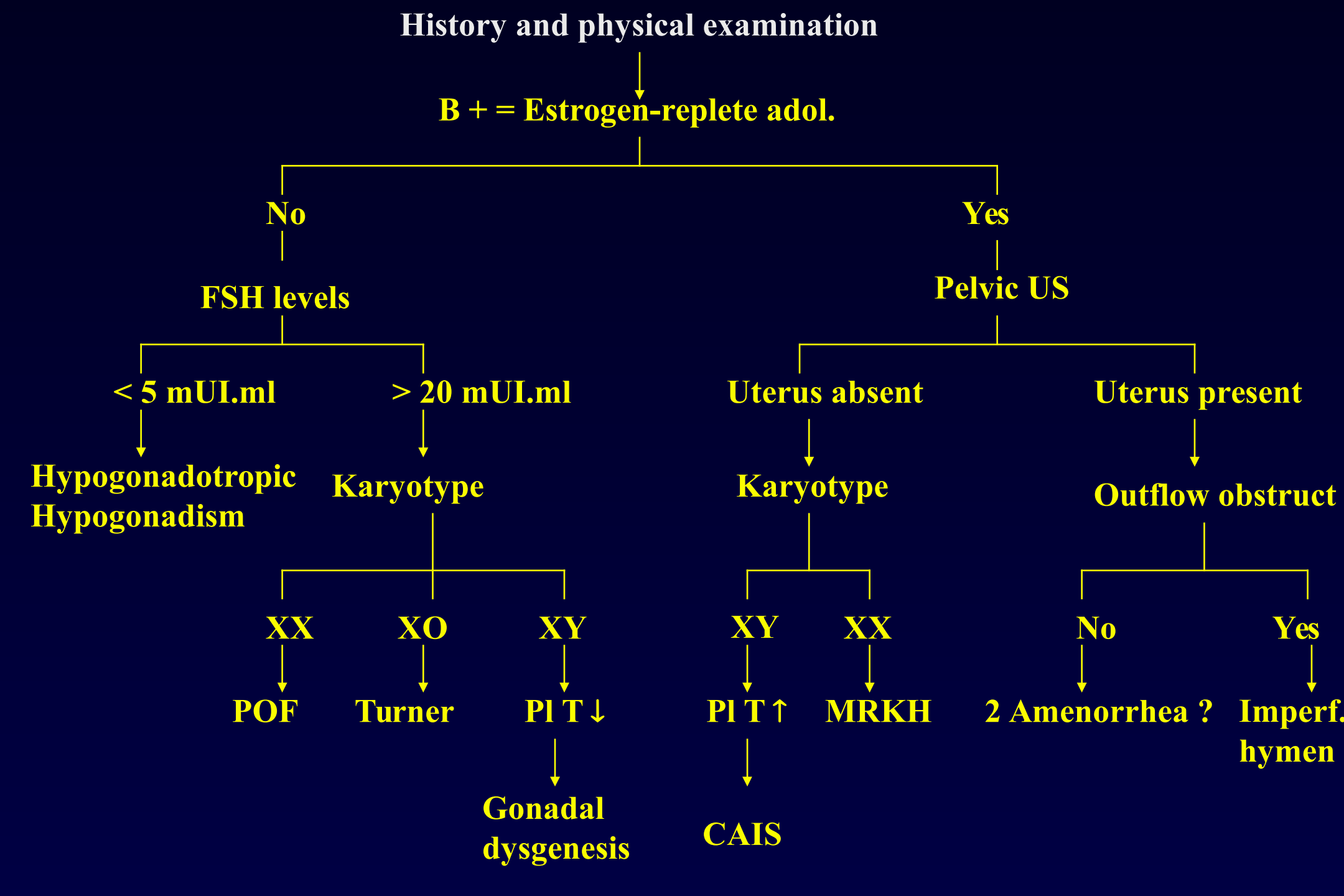
- chronic diseases
- anorexia
- weight loss
- excessive exercice
- stress / depression
- psychotropic drug abuse +/-

What are the causes of adolescent amenorrhea ?

* according to the initial examination
  - . +/- breast development
  - . +/- androgen excess
  - . +/- galactorrhea
  - . +/- weight loss
  - . +/- growth failure

* according to the laboratory test (FSH levels)
  - . hypergonadotropic hypogonadism
  - . Hypogonadotropic hypogonadism
  - . eugonadism

* according to Karyotype
  - - XX
  - - XO
  - - XY


History and physical examination
B + = Estrogen-replete adol.
No
Yes
FSH levels
Pelvic US
< 5 mUI.ml
> 20 mUI.ml
Uterus absent
Uterus present
Hypogonadotropic Hypogonadism
Karyotype
Karyotype
Outflow obstruct
XX
XO
XY
XY
XX
No
Yes
POF
Turner
Pl T↓
Pl T↑
MRKH
2 Amenorrhea ?
Imperf. hymen
Gonadal dysgenesis
CAIS

XY Adolescent amenorrhea

- not an exceptional condition

- XY primary adolescent amenorrhea = prevalence range = 3 → 10 % (27 %)

- XY primary amenorrhea may be completely overlooked

- occurrence of gonadal tumors (40 %)

XY Adolescent amenorrhea

isolated / associated

plasma testosterone

LOW

1 + Gonadal dysgenesis

1. complete gonadal dysgenesis
2. partial gonadal dysgenesis
3. mixed gonadal dysgenesis
4. associated / malf.

2 + Defects in androgen synthesis

1. Leydig cell hypo / aplasia
2. congenital lipoid hyperplasia
3. 17 β - OHSD deficiency
4. 17 - OHase deficiency

HIGH

+ Defects androgen action

+ CAIS

+ 5α RD

+ nephrotic syndrome (Wilms T)

(resistant to treatment)

Denys-Drash Syndrome

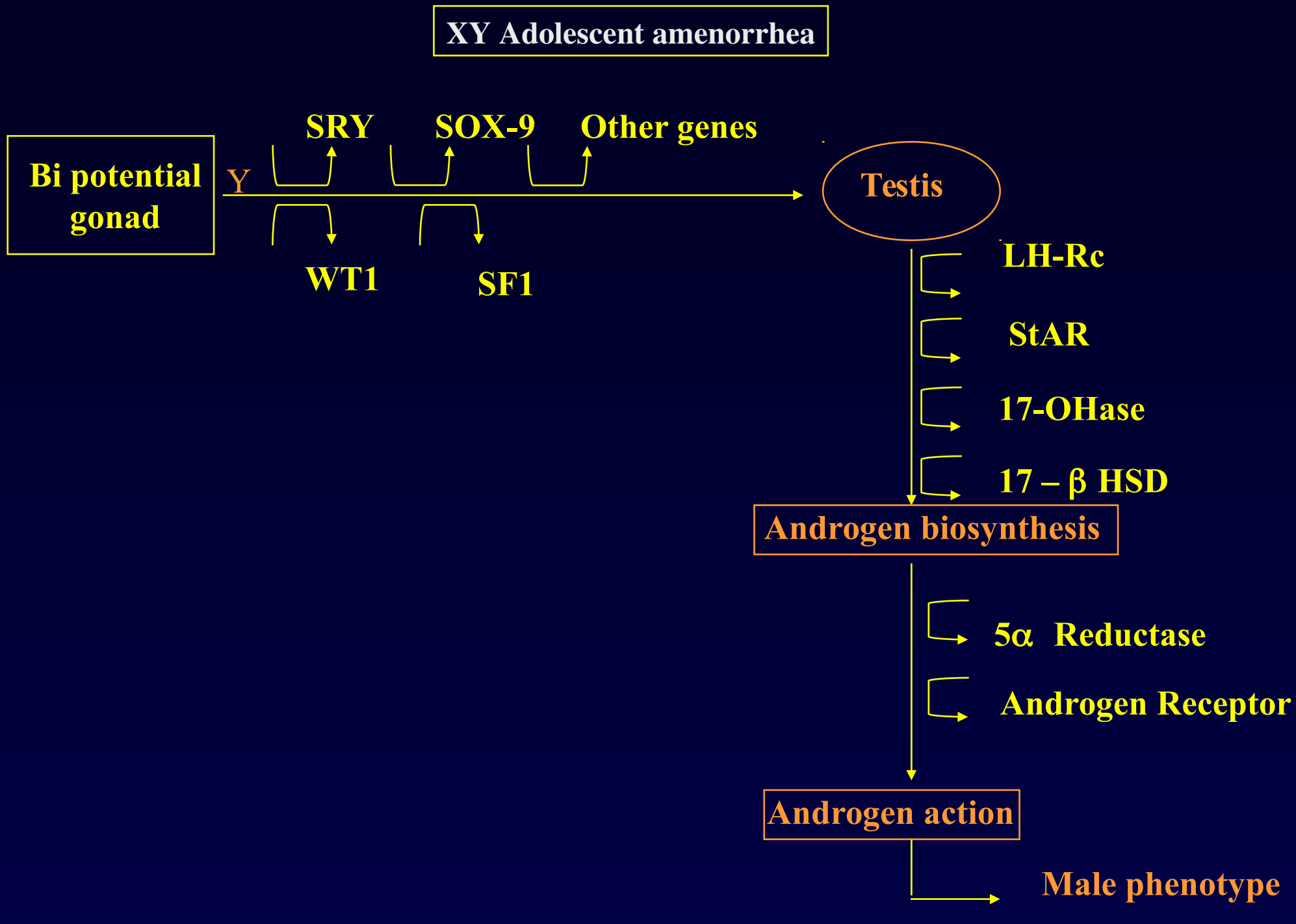
+ focal segmental glomerular sclerosis

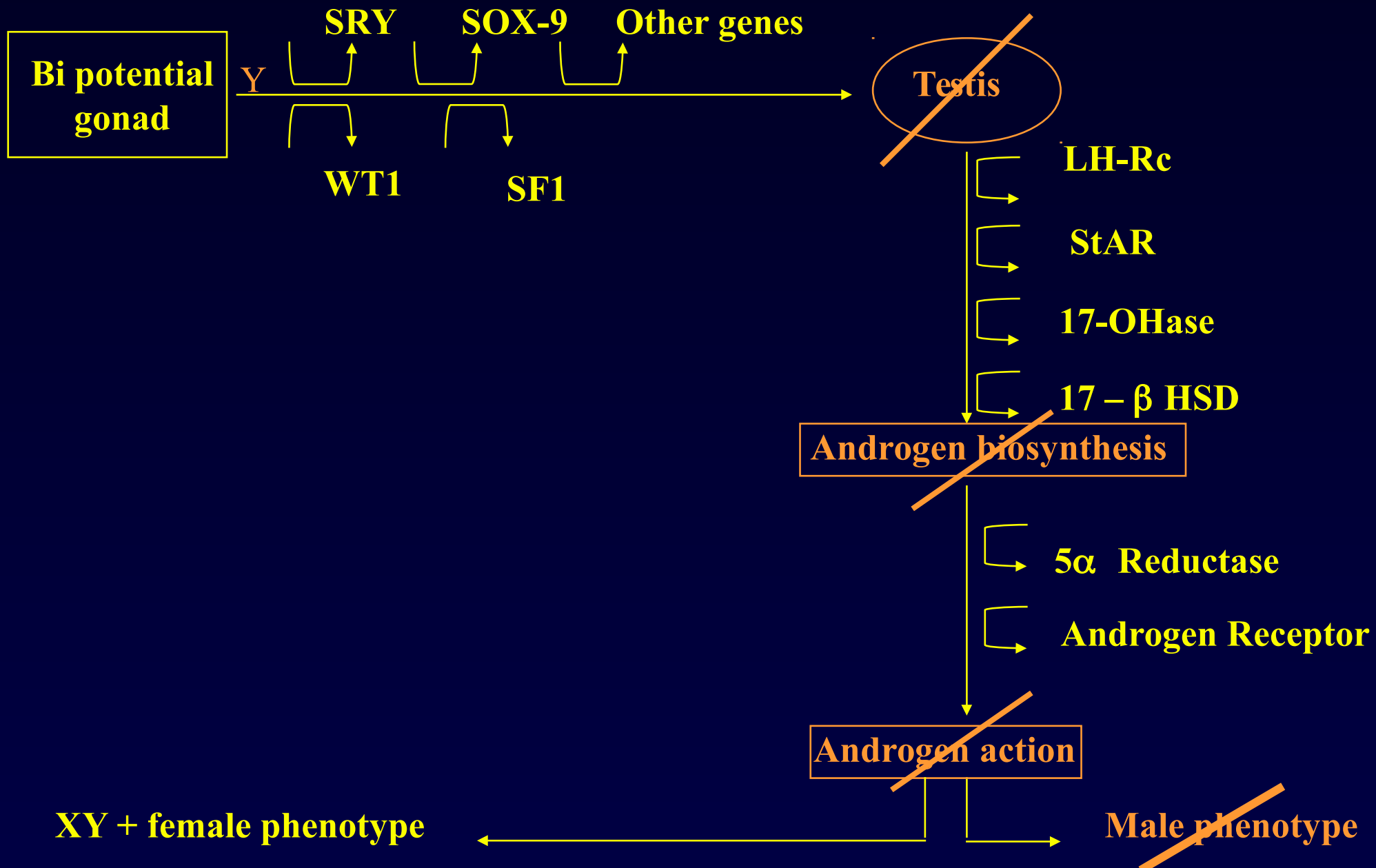
Frasier Syndrome

+ skeletal abnormalities

Campomelic dysplasia

+ mental retardation


XY Adolescent amenorrhea
Bi potential gonad
Y
SRY
SOX-9
Other genes
WT1
SF1
Testis
LH-Rc
StAR
17-OHase
17 – β HSD
Androgen biosynthesis
5α Reductase
Androgen Receptor
Androgen action
Male phenotype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Other genes
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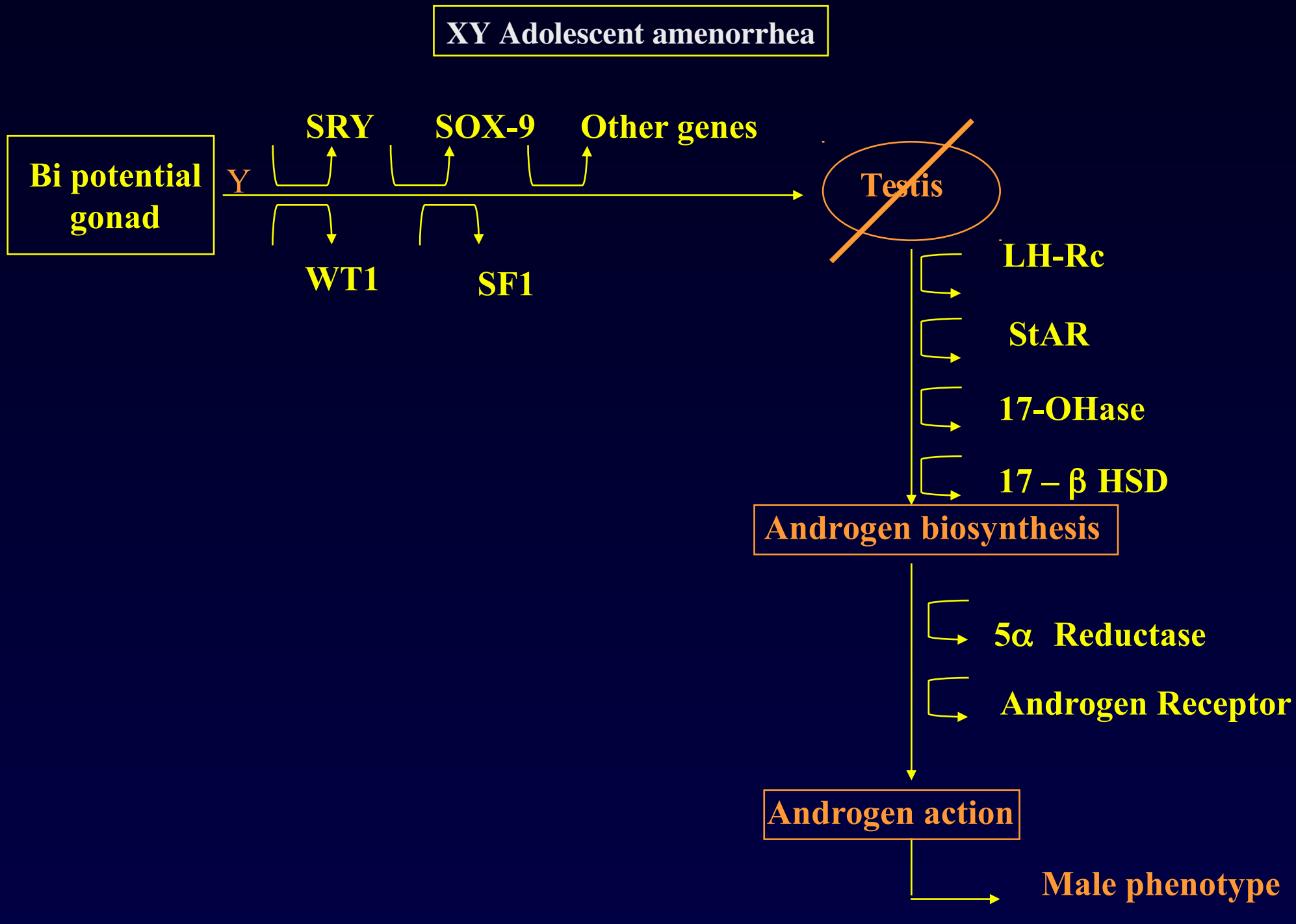
SF1
Testis
LH-Rc
StAR
17-OHase
17 – β HSD
Androgen biosynthesis
5α Reductase
Androgen Receptor
Androgen action
XY + female phenotype
Male phenotype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Androgen biosynthesis
5α Reductase
Androgen Receptor
Androgen action
Male phenotype

XY Adolescent amenorrhea

Complete gonadal dysgenesis (Swyer Syndrom or XY sex-reversal)

- . Bilateral streak gonad
- . Normally developped Mullerian ducts
- . Female external genitalia
- . Hyper GT hypogonadism, low E2 (low T)
- . Primary amenorrhea (absence of SSC)

→ XY-karyotype : 10 / 29 (34.5 %)

XY Adolescent amenorrhea

Complete gonadal dysgenesis in clinical practice: the 46,XY karyotype accounts for more than one third of cases

Vanessa Brito Campoy Rocha,[a] *Gil Guerra-Júnior, M.D., Ph.D.,*[a,b] *Antonia Paula Marques-de-Faria, M.D., Ph.D.,*[a,c] *Maricilda Palandi de Mello, Ph.D.,*[a,d] *and Andréa Trevas Maciel-Guerra, M.D., Ph.D.*[a,c]

[a] Grupo Interdisciplinar de Estudos da Determinação e Diferenciação do Sexo, [b] Department of Pediatrics, [c] Department of Medical Genetics, and [d] Centro de Biologia Molecular e Engenharia Genética, State University of Campinas, São Paulo, Brazil

Fertil and Steril, 2011, 96 ; 6 : 1431 - 1434

Clinical manifestations

16 year old adolescent girl : primary amenorrhea

Obesity: Weight: 79kg

Height: 162,7 cm

BMI: 30 kg/m²

Female phenotype

Pubertal status: B2-B3

P2-P3

A1

Laboratory data

FSH: 74 U/l (N 3-8 U/l)

LH: 20 U/l (N 1,5-6 U/l)

Estradiol: 11 pg/ml (N 25-100 pg/ml)

Testosterone: 0,3ng/ml (N <0,6 ng/ml)

Prolactin: 6,6 ng/ml (N 3-20 ng/ml)

Pelvic ultrasonography: Gonad and uterus were not seen

Karyotype: 46 XY

→ 46 XY sex reversal

SRY gene analysis

Evolution:

Coelioscopy: atrophic uterus and two adnexia which were like ovaries

AMH: not detectable

Bilateral gonadectomy left side: fibrous ovarian tissue without follicle

right side: beginnings of ovarian tissue

gonadoblastoma

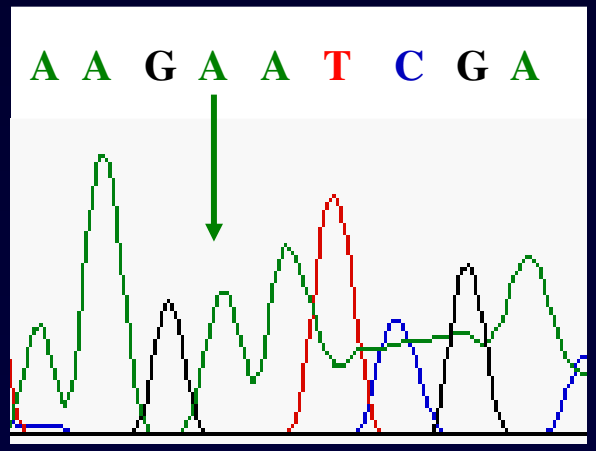
F. Paris et al, Fert Steril. 2009

DNA extraction: blood
PCR of the SRY gene
Automatic sequencing

Y 129 N mutation (in the HMG box)

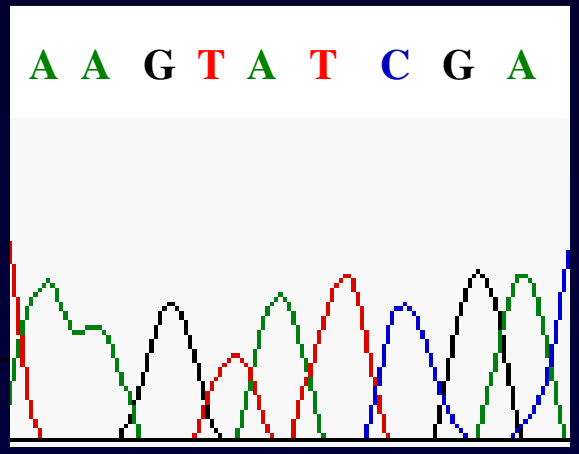
Patient

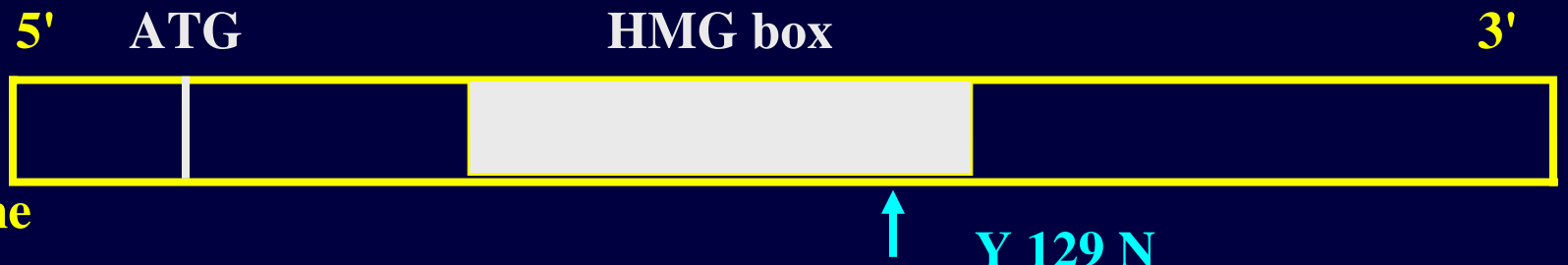
K N R
128 129 130



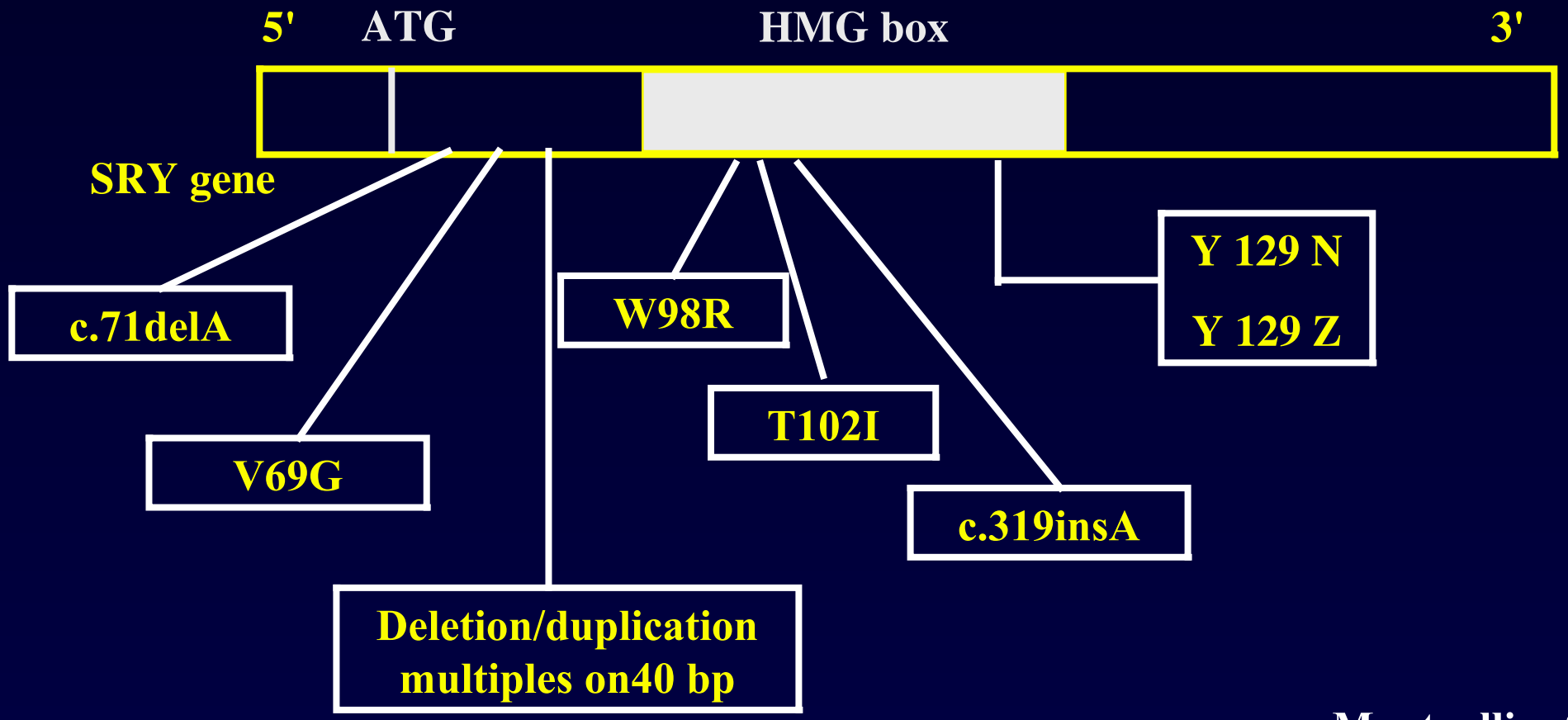
Patient's father

K Y R
128 129 130





Mutations of SRY



Montpellier 2012

XY Adolescent amenorrhea

Complete gonadal dysgenesis / Swyer syndrome

. management

1. induction of puberty + estrogens administration

2. combined estrogens + progesterone

development and growth of the uterus

. gonadectomy + salpingectomy (laparoscopy)

* successful pregnancy (egg donation) exceptional

Gonadal dysgenesis + renal abnormalities

1. Denys-Drash Syndrome
   - early onset nephrotic syndrome + hypertension
   - progression to end-stage renal failure + Wilm T.
   ± ambigous genitalia / sex reversal

2. Frasier Syndrome
   - focal segmental glomerular sclerosis
   - female phenotype + primary amenorrhea
   - bilateral gonadectomy / risk of gonadal malignancy

WT1 mutation

Clinical manifestations

15 y old girl = "delayed" puberty
absence of feminization

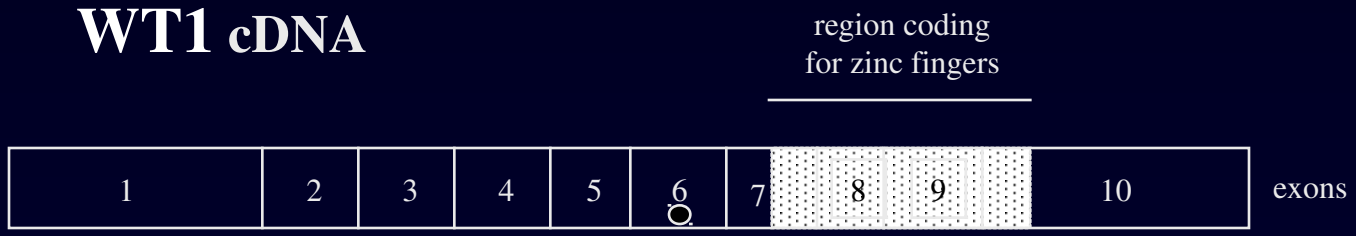
Personal antecedents

- ambiguous genitalia / neonatal period
- N testosterone response HCG
- 46 XY
- DIS = « Complete » AIS
  → bilateral gonadectomy
- 13y = proteinuria

Molecular biology studies

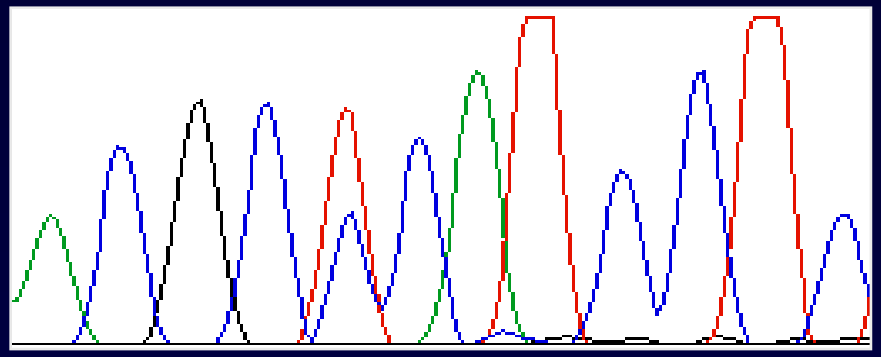
- AR gene sequence = N
- 5aR gene sequence = N
- WT1 gene sequence ?

WT1 cDNA

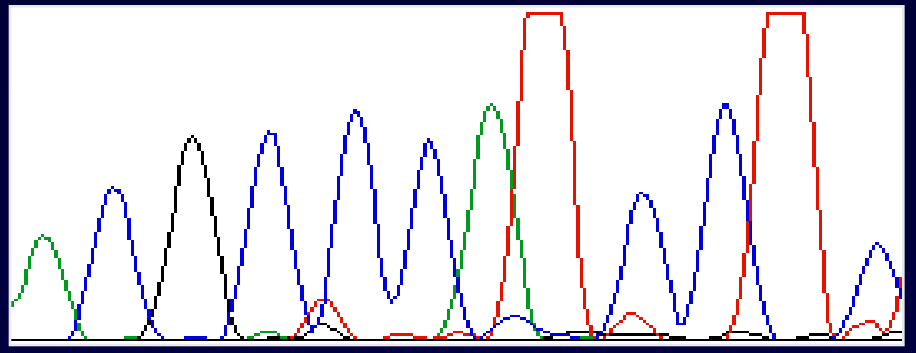


T	P/L*	P	L
278	279	280	281
A C G	C C/T*C	A T C	C T C

T	P	P	L
278	279	280	281
A C G	C C C	A T C	C T C

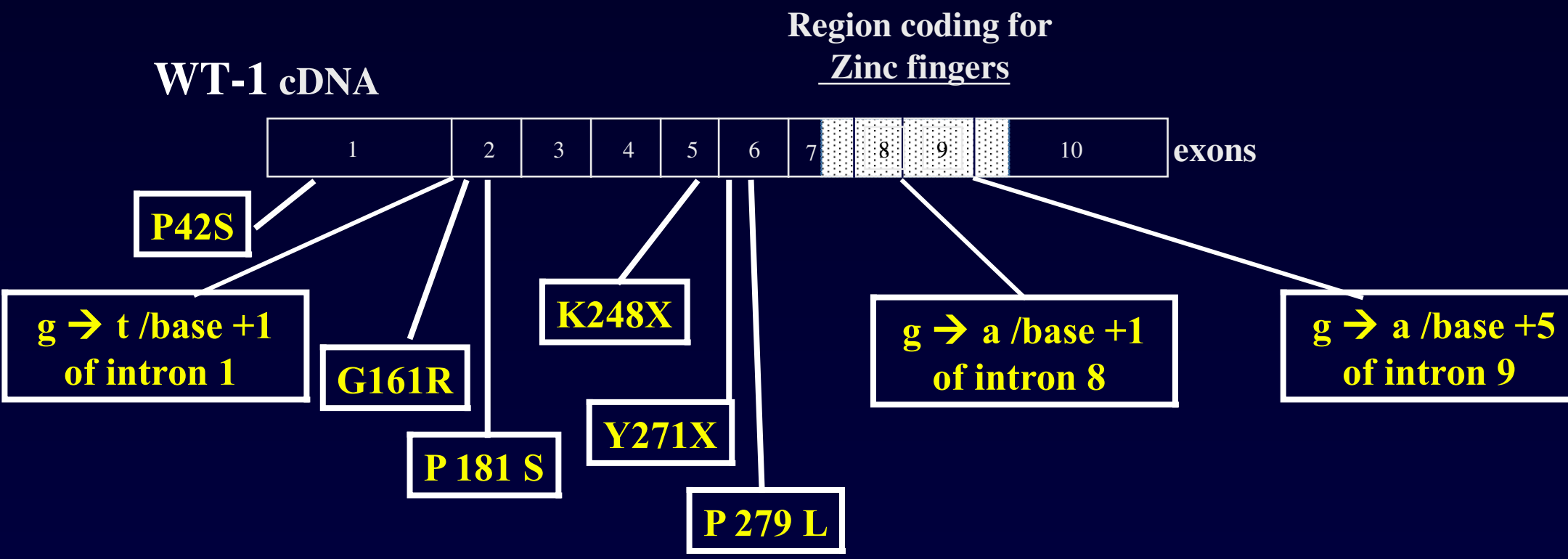


patient



control

Mutations of WT-1



Montpellier 2012

46,XY Complete Gonadal Dysgenesis

Genetic causes:

1. **SRY: 10 – 20 %**
2. **WT1 (Rarely isolated 46,XY CGD)**
3. **SF1 %??**

AIM: Study the frequency of SF1 gene abnormalities in 46,XY CGD

Philibert et al. Reproductive Biology and Endocrinology 2010, 8:28
http://www.rbej.com/content/8/1/28

REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY

RESEARCH Open Access

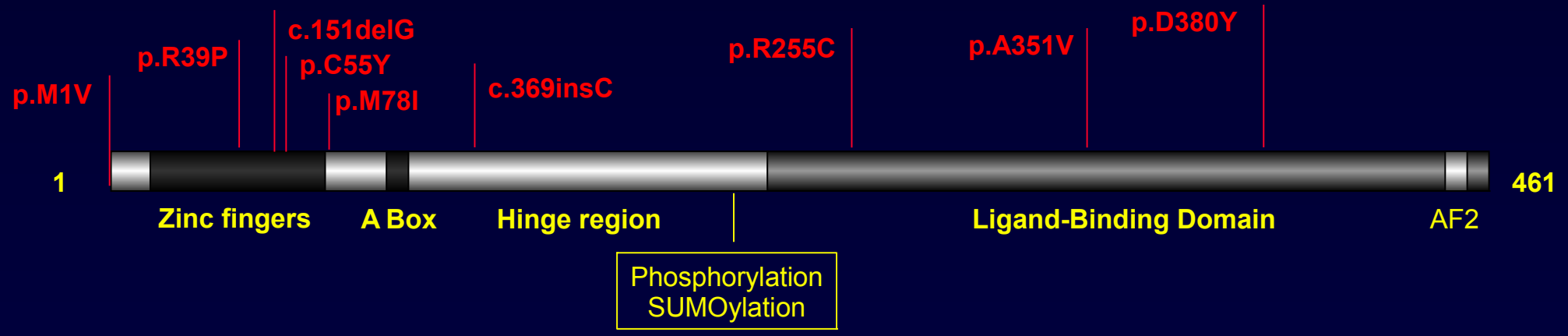
Steroidogenic factor-1 (SF-1) gene mutation as a frequent cause of primary amenorrhea in 46,XY female adolescents with low testosterone concentration

Pascal Philibert[1†], Elodie Leprieur[1,2†], Delphine Zenaty[3], Elisabeth Thibaud[4], Michel Polak[4], Anne-Marie Frances[5], James Lespinasse[6], Isabelle Raingeard[7], Nadège Servant[1], Françoise Audran[1], Françoise Paris[1,2], Charles Sultan[1,2*]

Aménorrhées primitives de l'adolescente

Primary amenorrhea (n=45)

XY Primary amenorrhea / gonadal dysgenesis
+ Absence of Breast development
+ Pubic hair: P3-P4 (P5)
+ Low plasma Testosterone <50 ng/dl
+/- Uterus development



SF1 gene mutation is a frequent cause of - primary amenorrhea 9/45
- complete gonadal dysgenesis

Philibert P *et al.* Rep Biol Endo, 2010

+ unpublished data

Mutations in the *Desert hedgehog* (*DHH*) Gene in Patients with 46,XY Complete Pure Gonadal Dysgenesis

P. CANTO, D. SÖDERLUND, E. REYES, AND J. P. MÉNDEZ

Patient	Age (yr)	Gonads	External genitalia
1	17	Bilateral streaks	Female
2	19	Bilateral streaks with bilateral gonadoblastoma	Female
3	25	Bilateral streaks	Female
4	16	Bilateral streaks	Female
5	13	Bilateral streaks with bilateral gonadoblastoma	Female
6	26	Bilateral streaks with bilateral dysgerminoma	Female

J Clin Endocrinol Metab, September 2004, 89(9):4480–4483

Ovaries and Female Phenotype in a Girl with 46,XY Karyotype and Mutations in the *CBX2* Gene

Anna Biason-Lauber,[1,2,*] Daniel Konrad,[1,2] Monika Meyer,[1] Carine deBeaufort,[3] and Eugen J. Schoenle[1,2]

* **In mice targeted ablation of M33, an ortholog of *Drosophila* Polycomb**

  ⟶

* **In 1 patient**

  1 – XY sex reversal

  2 – normal uterus, vagina development

  3 – normal ovarian tissues (primordial follicules)

  4 – low basal, HCG / plasma T

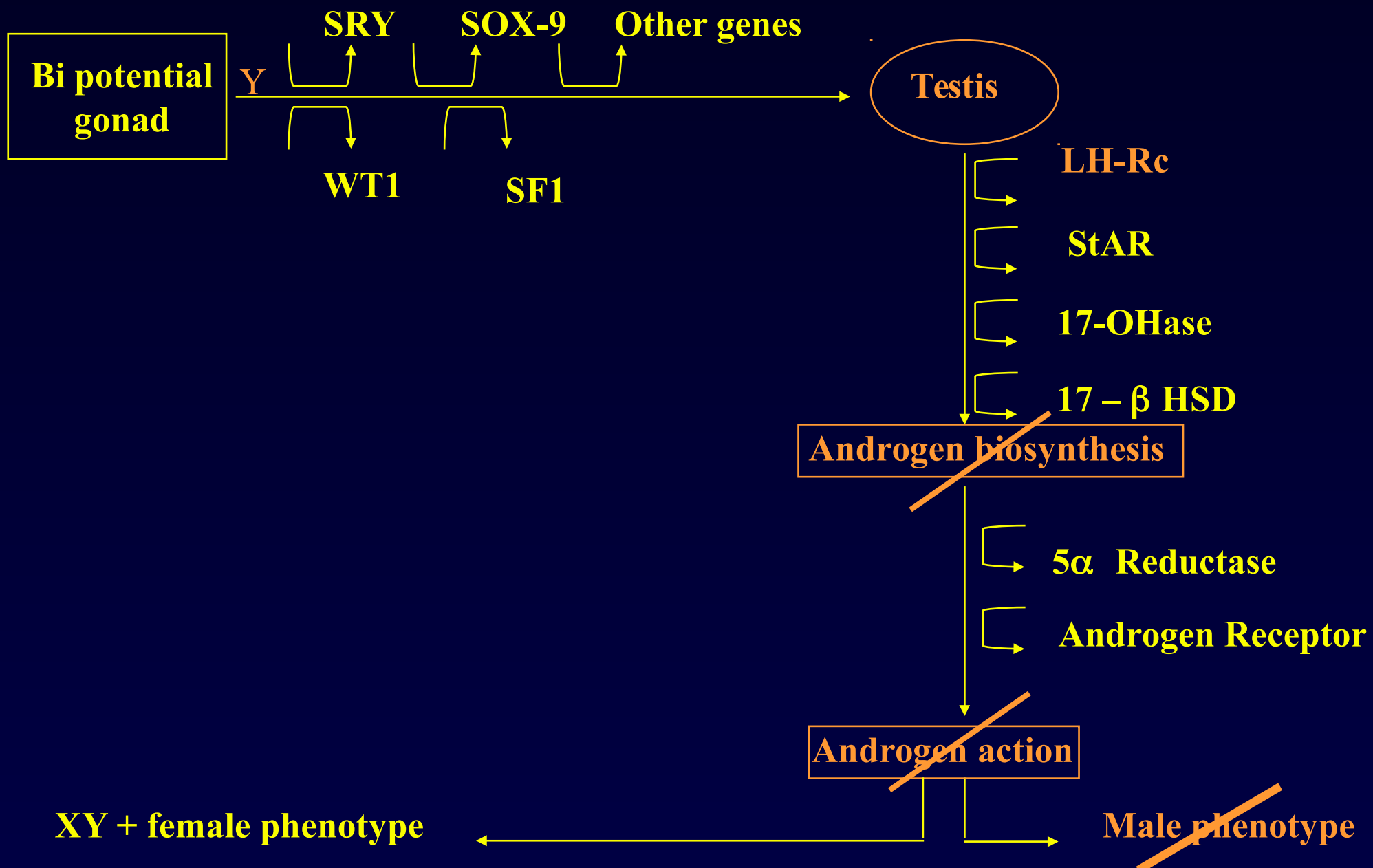
  5 – indetectable AMH

  ⟶ **SRY, SOX9, SF1 sequences = normal**

  ⟶ **CBX2 gene = C293T / G1370C**

The American Journal of Human Genetics *84*, 658–663, May 15, 2009

Aménorrhées primitives de l'adolescente



LH receptor defects

Large phenotypic spectrum : female external genitalia →
ambiguous genitalia → micropenis

+ Leydig cell aplasia

mutation within the LH-Rc gene

↳

+ Leydig cell hypoplasia

mutation within the LH-Rc gene

↳

Clinical manifestations

9 yr.

- **female phenotype**
- **inguinal hernia**
- **blind vaginal pouch**
- **no Müllerian derivatives**
- **46,XY sex reversal**

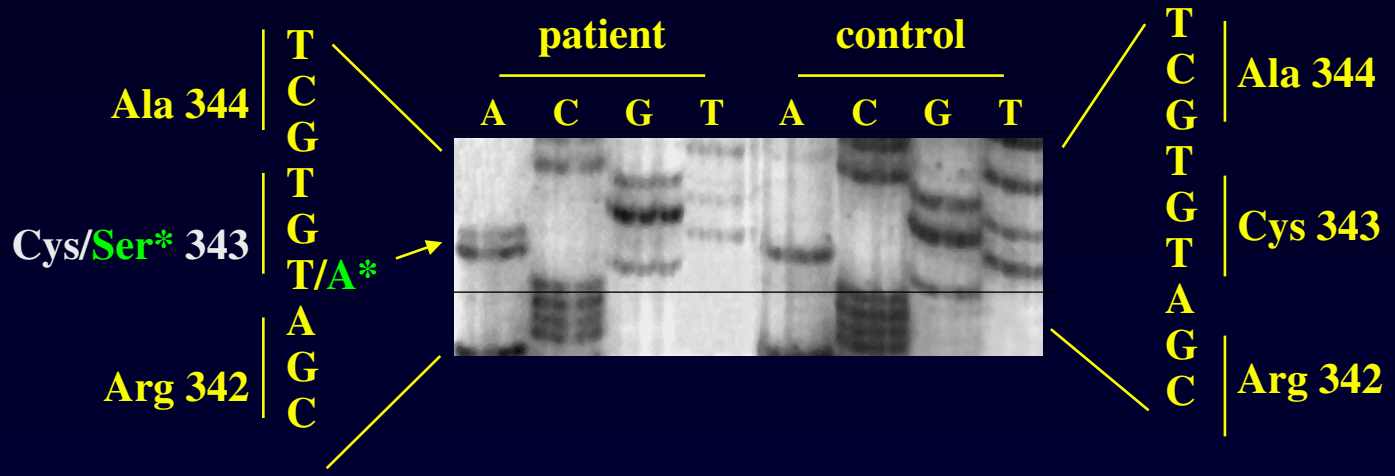
complete androgen insensitivity ?

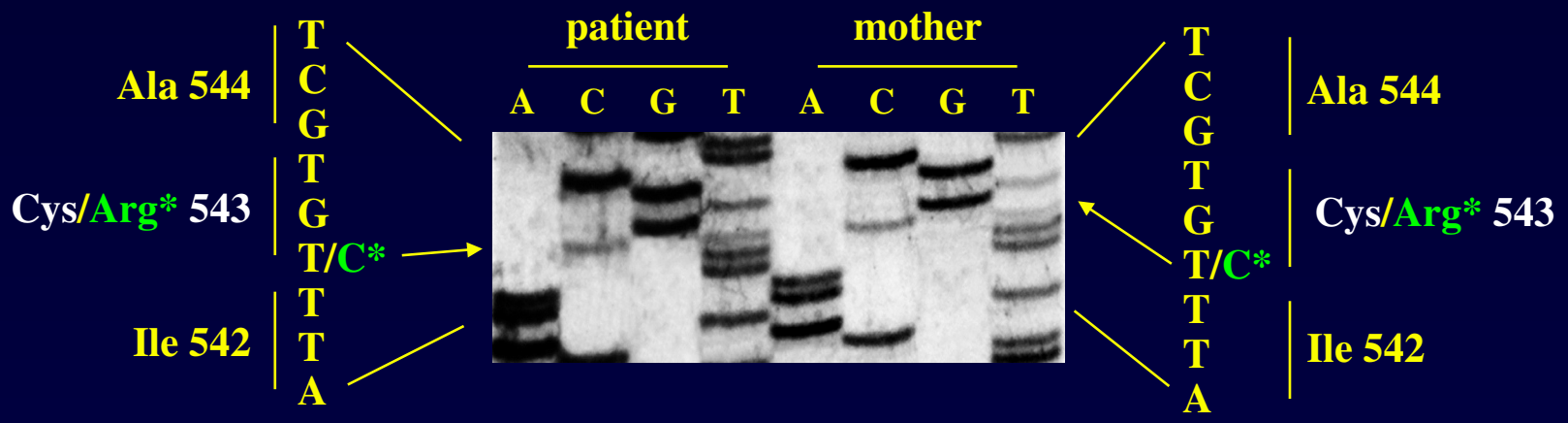
14 yr.

- **no breast development, amenorrhea**
- **low basal testosterone. → after HCG**
- **high basal LH. ↑↑ after GnRH**
- **testis: rare Leydig cells**

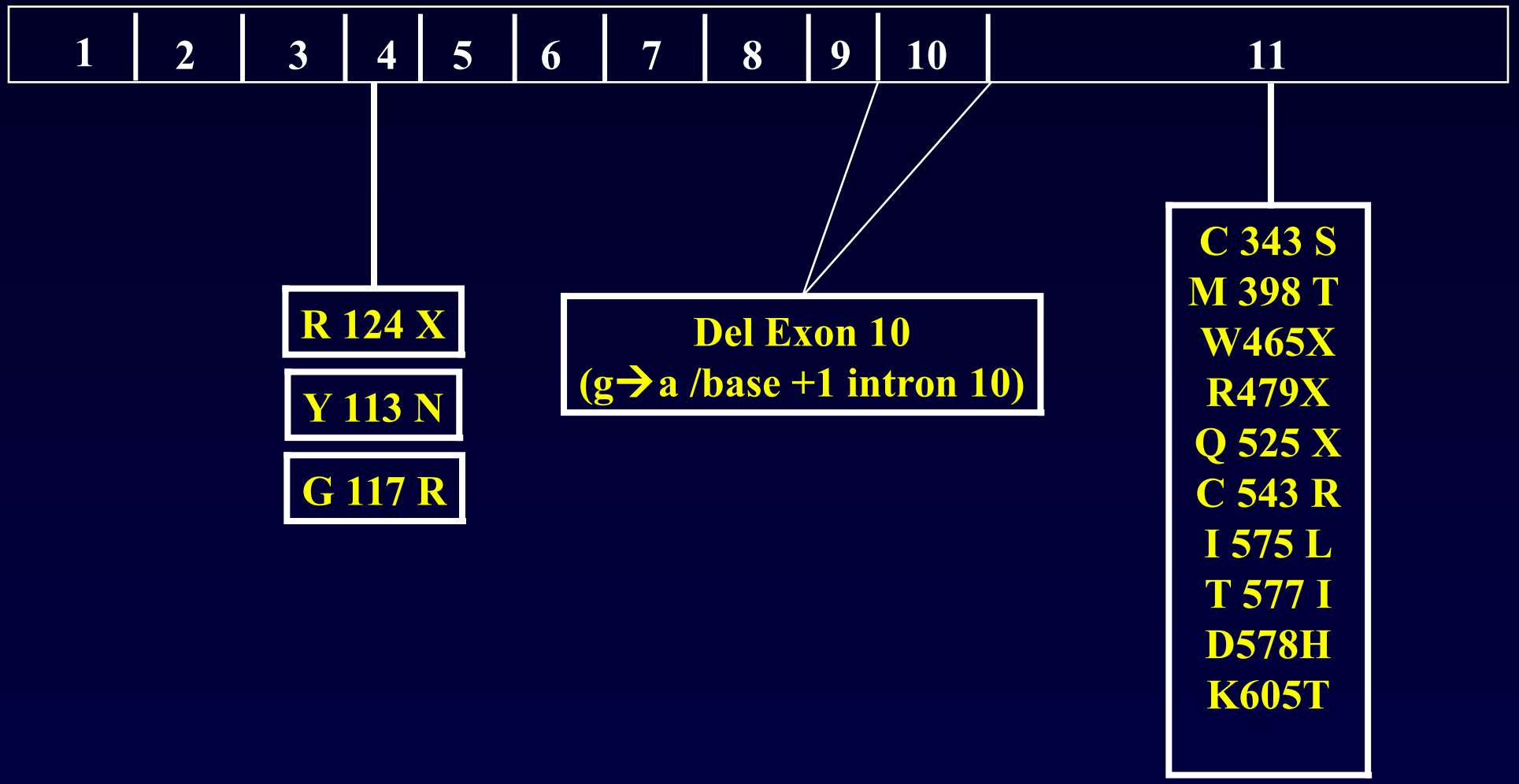
Leydig cell hypoplasia

└→ LH.Rc gene mutation ?


patient
control
A C G T A C G T
Ala 344
Cys/Ser* 343
Arg 342
T C G T G T/A* A G C
T C G T G T A G C
Ala 344
Cys 343
Arg 342


patient
mother
A C G T A C G T
Ala 544
Cys/Arg* 543
Ile 542
T C G T G T/C* T T A
T C G T G T/C* T T A
Ala 544
Cys/Arg* 543
Ile 542

Mutations of LH Receptor



Montpellier 2012

XY Adolescent amenorrhea

17α -hydroxylase deficiency

clinical manifestations

- pubertal failure, tall height
- amenorrhea
- Hypertension

bioch diagnosis

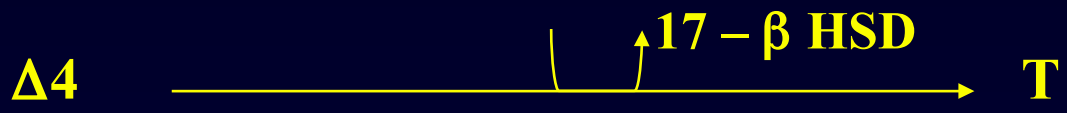
- Low 17OHP rog / high prog (Syn. test.)

genetic analysis

- point mutations of the p450 C17 gene
  - S.106 P → 0 activity
  - T 132 S → ↓ activity
- Stop codon 120 → 0 activity
- Stop codon 387 → ?

XY Adolescent amenorrhea

17β OH steroid dehydrogenase deficiency



consanguinity, ethnic groups

female phenotype → reared as female

Pubertal virilization +

Diagnosis

↓ T / Δ4 ratio

Molecular analysis of the 17β OHSD gene

Mini Review

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr 2010;74:229–240
DOI: 10.1159/000318004

Received: December 11, 2009
Accepted: June 23, 2010
Published online: August 3, 2010

The Clinical and Molecular Heterogeneity of 17βHSD-3 Enzyme Deficiency

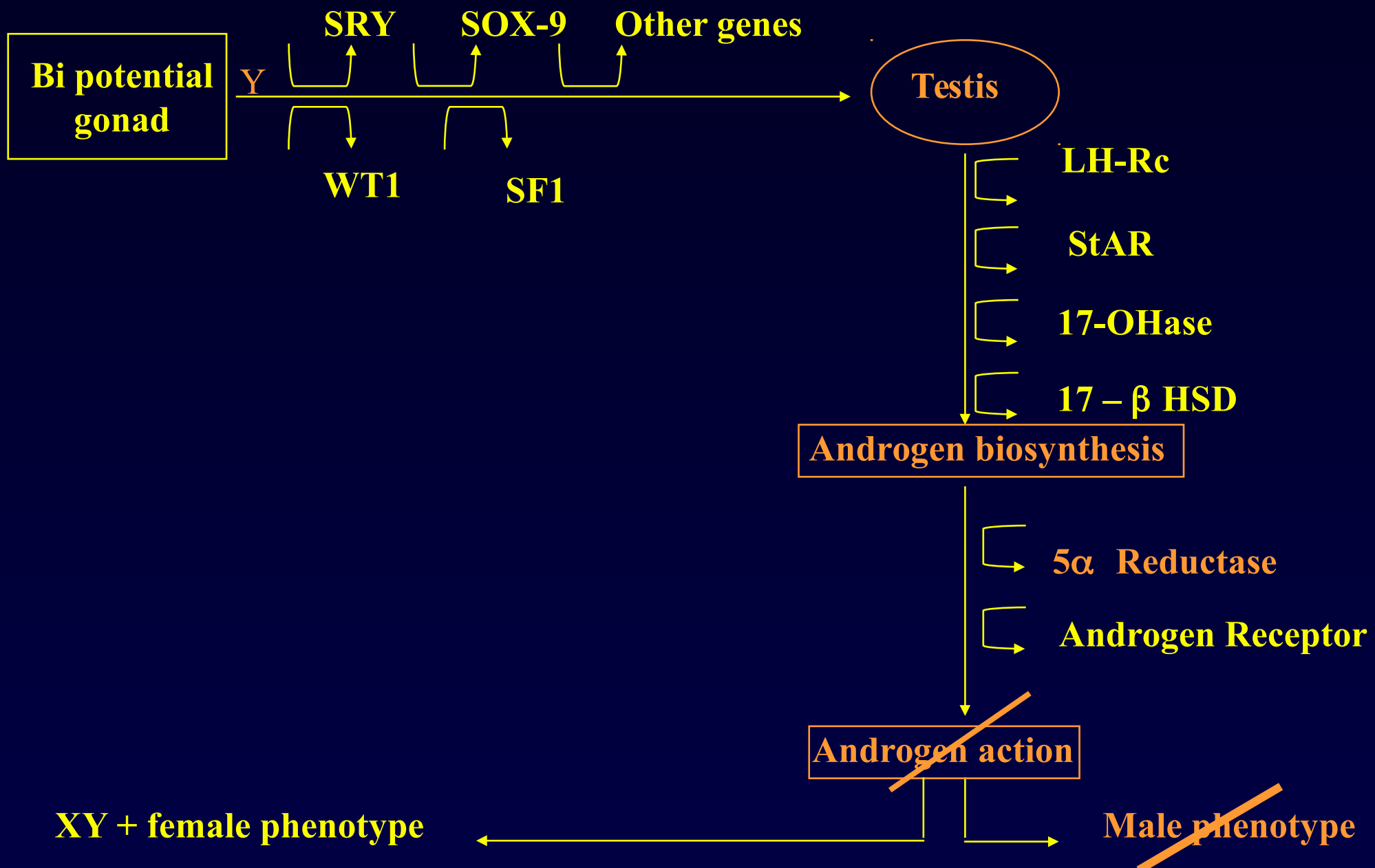
Minu M. George[a] Maria I. New[b] Svetlana Ten[a] Charles Sultan[c]
Amrit Bhangoo[a]

Clinical presentation + early childhood / difficult
. girls + inguinal hernia
. mild clitoromegaly
. single urethral opening
+ adolescence
. primary amenorrhea
. virilization
. female/male gender role

Biochemical abnormality : low T/D4 ratio (± HCG)

Mol. genetics : mutations / 17β HSD-3

Aménorrhées primitives de l'adolescente



5α Reductase deficiency

- female phenotype

- primary amenorrhea

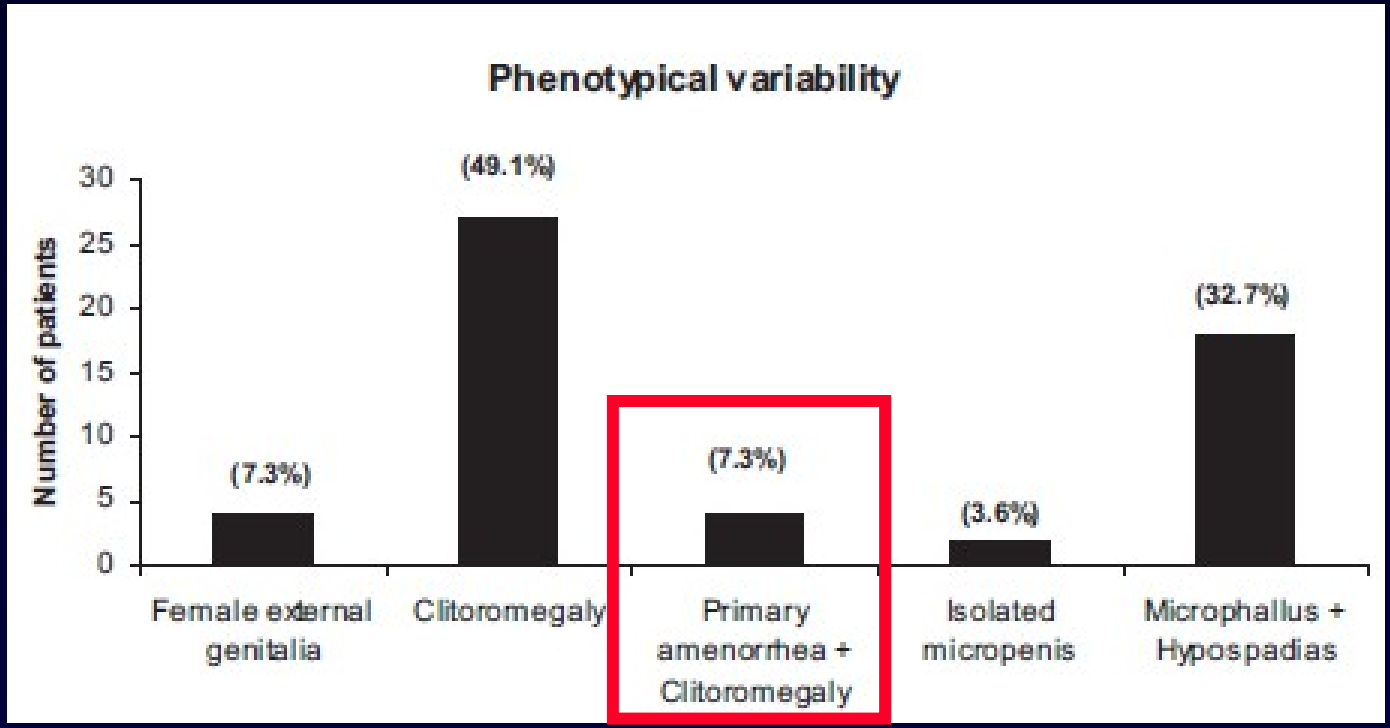
- virilization at puberty ++

Diagnosis

- ↑ T / DHT ratio

- Molecular analysis of the 5α Reductase gene

5 α reductase deficiency



Phenotypical variability of the 55 patients with 5α-reductase - type 2 deficiency.

Maïmoun L. *et al.* JCEM; feb 2011

Primary amenorrhea in four adolescents revealed 5α-reductase deficiency confirmed by molecular analysis

Laurent Maimoun, Ph.D.,[a] Pascal Philibert, Pharm.D., Ph.D.,[a] Philippe Bouchard, M.D., Ph.D.,[b] Gönül Öcal, M.D.,[c] Bruno Leheup, M.D., Ph.D.,[d] Patrick Fenichel, M.D., Ph.D.,[e] Nadège Servant, Ph.D.,[a] Françoise Paris, M.D., Ph.D.,[a,f] and Charles Sultan, M.D., Ph.D.[a,f]

Main clinical, hormonal, and molecular data from four patients with primary amenorrhea and 5α-reductase deficiency.

Patient	Age (y)	Ethnic origin	Phenotype	Parental consanguinity	Sex of rearing	Basal plasma T (nmol/L)	Basal plasma DHT (nmol/L)	Basal plasma T/DHT ratio	*srd5A2* mutations
1	18	Turkish	CM + perineoscrotal hypospadias + no breast development	Positive	F	22.4	ND	ND	Exon 1: p.L55Q (homozygote)
2	24	Tunisian	CM + penoscrotal hypospadias + no breast development	Positive	F to M	16.2	0.9	18	Exon 1: p.Q56R (homozygote)
3	18.5	African	CM + no breast development	Negative	F	21.5	8.6	2.5	Exon 4: p.N193S (homozygote)
4	15.7	French	CM + no breast development	Negative	F	23.2	0.55	42.1	Exon 1: c.34delG; Exon 5: p.R246W (compound heterozygote)

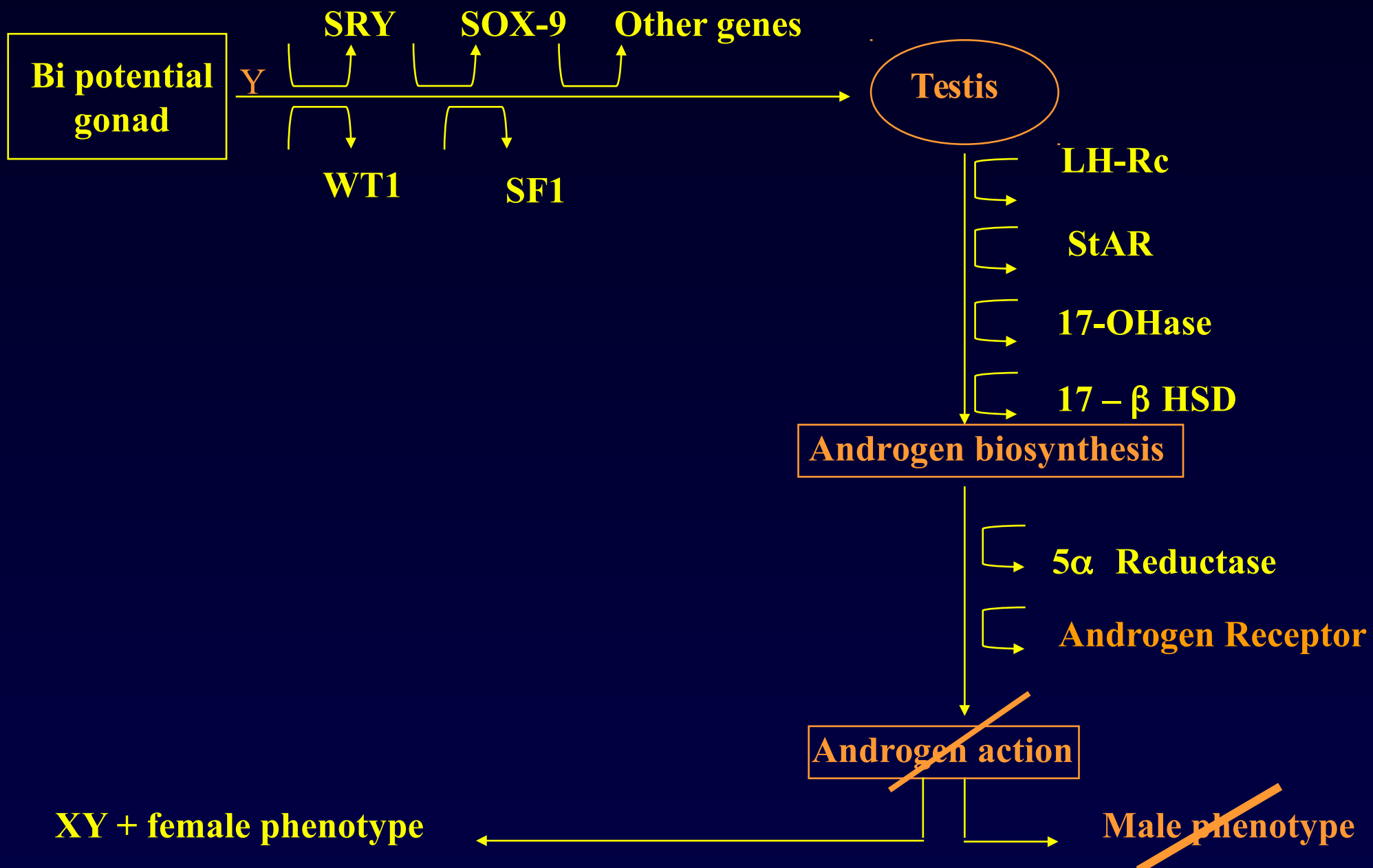
Fertility and Sterility, 2011, 95 (2) : 804.e1-5

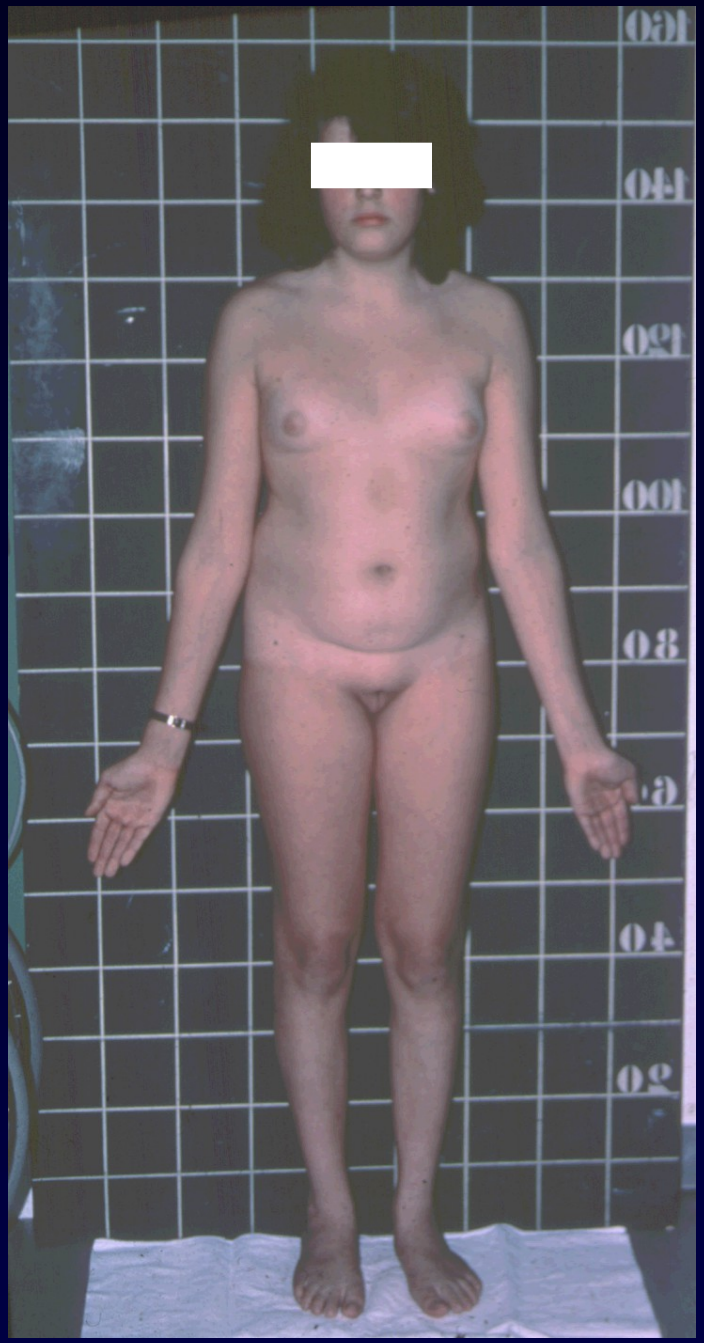
Molecular diagnosis of 5a reductase deficiency In 4 elite young female athletes through hormonal screening for hyperandrogenism.

P Fenichel, F. Paris… and Ch Sultan

JCEM 2013

Aménorrhées primitives de l'adolescente





Complete androgen insensitivity syndrome

. the most common of conditions leading to the presentation of an XY adolescent female (1/50 000 birth)

. associated with normal breast development

. absence of pubic and axillary hair growth

. The testis may be palpable with the inguinal canal or even within labia majora

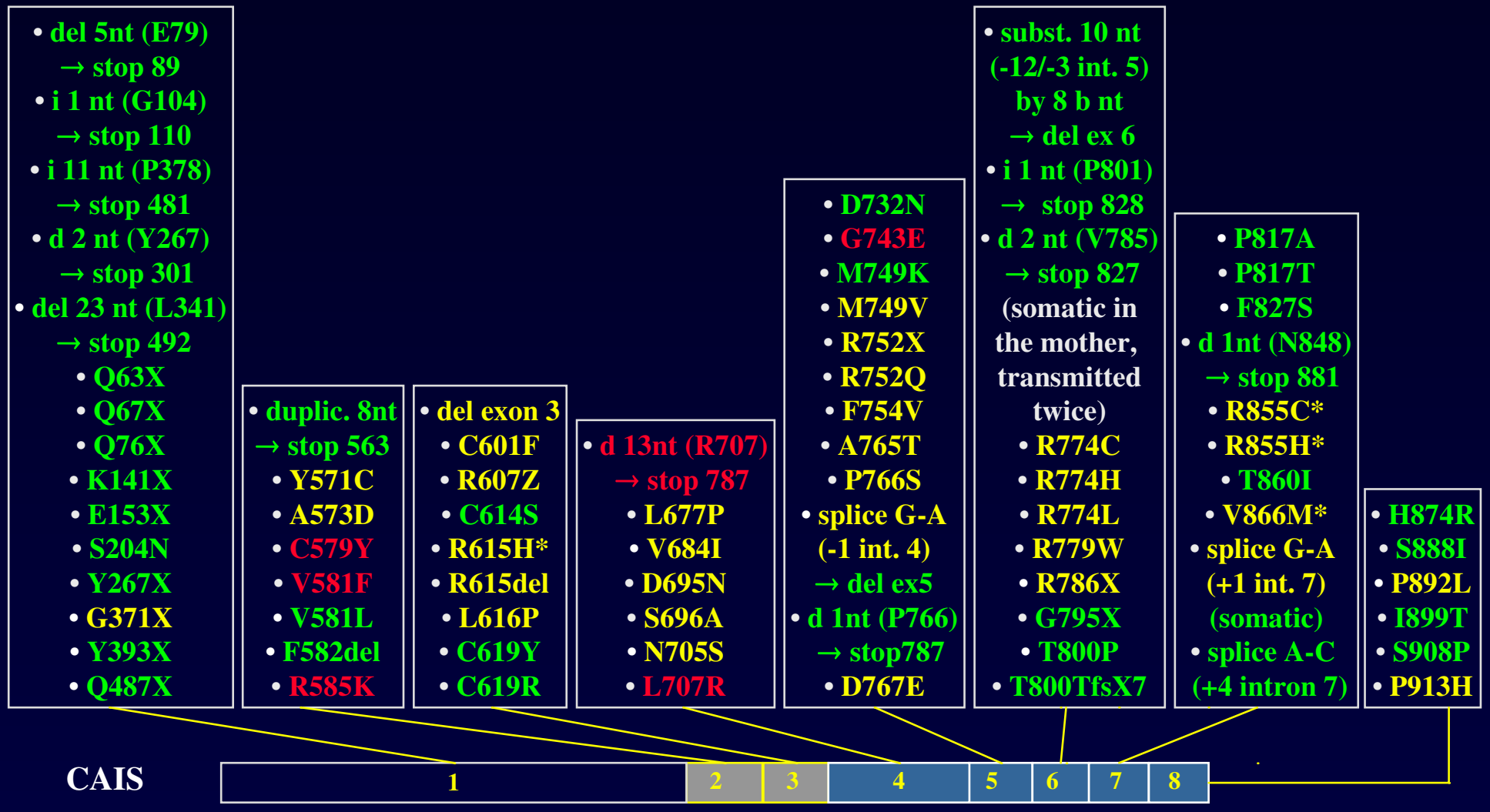
. Diagnosis : - high plasma T

- high plasma AMH

- N/high plasma LH

- molecular analysis of the AR gene

Androgen receptor mutations identified in Montpellier: CAIS



heterogeneity, number ++

(Sept 2012)

XYAdolescent amenorrhea

Complete androgen insensitivity syndrome

. gonadectomy / performed as early as possible

- to avoid psychological concerns
- to reduce the risk of gonadoblastoma development

. Adolescent with CAIS = female gender identify + female heterosexual orientation

. vaginal dilatation is usually effective

XY Adolescent amenorrhea

Personal experience (Montpellier University Hospital)

2007 – 2012 = 5 yrs (Primary amenorrhea n = 121)

N = 34 - XY

Pl T > 5 ng.ml
N = 19
Androgen resistance ?

- **AR gene mutation = n = 15**
- **5αR deficiency = n = 2**

Pl T < 0.5 ng.ml
N = 15
Complete gonadal dysgenesis ?

- **SRY gene mutation = n = 2**
- **SF1 gene mutation = n = 6**
- **LH-RC gene mutation = n = 1**

Aménorrhées primitives de l'adolescente

Secondary amenorrhea

1. systemic
   - chronic diseases / weight loss
   - excessive exercise
2. hypothalamo / pituitary disorders
   - tumors
   - cranial irradiation
   - hyperprolactinimia
3. endocrine disease
   - PCOS
   - other endocrine diseases
4. ovarian dysgenesis
5. Gestation!

Aménorrhées primitives de l'adolescente

1 - Introduction

2 - Causes of adolescent amenorrhea

3 – Announcement of diagnosis

4 – Psychological support

5 - Treatment

6 - Conclusion

Disclosure of diagnosis

in the past, concealment of diagnosis and treatment information from patients was the standard practice

→ it is now established practice to disclose the diagnosis and its etiology

this is usually gradually done in adolescence, depending on the level of understanding and knowledge

disclosure of diagnosis allow better compliance with medical treatment

→

allows for other members of the family to be screened

→

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Cultural perceptions and practices around menarche and adolescent menstruation

Menstruation can be described as a Dr Jekyll and Hyde phenomenon !

It carries both a good and a bad reputation

- **A « good reputation » = importance of menarche as a sign of maturity and fertility**
- **A « bad reputation » as physically and psychologically problematic persist**

→ It's a challenge to promote menstruation on a vital sign of healthy functionning

Psychological problems

- Danish study (Johannsen TH. EJE (2006))

  XY adolescent female

  - suicidal thoughts : increased

  - psychological / psychiatric problems ++

- No developmental disorders

- Education / intelligence quotient = N. females

Aménorrhées primitives de l'adolescente

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Treatment

1. Permanent amenorrhea (Cong)

= protocol of estrogenization

dev. / maintenance of sec. Sex. Characteristics

dev. / maturation of internal genital organs

improvement of bone mass

± cardiovascular prevention

Treatment

2. Protocol of estrogenization

= estrogen therapy must begin with low, continue and progressively increasing doses

→ natural estrogens (17β estradiol) = 0.2 mg – 2 mg /d

0.2 mg/d x 6 m – 12 m (24 d)

0.4 mg/d x 6 m – 12 m (24 d)

→ progesterone

didroprogesterone 10 mg (day 10-24)

chlormadinone AC 5 mg/d (day 10 – 24)

→ combined OC

Induction of puberty per os

Treatment with 17β-estradiol in an increasing dose schedule every 6 months:

- 5 μg/kg per day p.o.
- 10 μg/kg per day p.o.
- 15 μg/kg per day p.o.
- 20 μg/kg per day p.o.
- Adult dose at about 2 mg per day

Treatment with ethinyl estradiol in an increasing dose schedule every 6 months:

- 0.1 μg/kg per day p.o.
- 0.2 μg/kg per day p.o.
- 0.4 μg/kg per day p.o.
- 0.6 μg/kg per day p.o.
- Adult dose is about 30 μg per day. Then a contraceptive pill can be used

After 1 to 2 years of substitution with estrogens, a progestin is added to prevent endometrial hyperplasia (mammary gland Tanner IV).

Delemarre EM, 2008, Eur. J. Endocrinology

Treatment

1. Hormone remplacement therapy
   - pubertal development
   - psychological reasons

2. Vaginal hypoplasia
   - non-surgical pressure dilatation

3. Allogenic oocytes (uterus +)
   → pregnancy

New developments :

1 – molecular genetics

- GWAS → locus 8q22.3 (Quin)
- GWL → 2 loci chr.7 (Fellous)
- Mutations in LARS2 (Mit Leucyl tRNA synthase) (Pierce)
- CITED2 Mutations: 1 variants (Koopman)
- AR ?

2 – hormonal investigations

- AMH evaluation (Themmen)

Anti-Müllerian hormone: an ovarian reserve marker in primary ovarian insufficiency

Jenny A. Visser, Izaäk Schipper, Joop S. E. Laven and Axel P. N. Themmen

AMH as a marker for primary amenorrhea

- idiopathic amenorrhea
→ undetectable AMH level

- genetic amenorrhea
→ FMR1 premutation: AMH 50% lower
→ Turner Syndrome: AMH // mosaicism

-autoimmune amenorrhea
→ AMH +/- normal

Aménorrhées primitives de l'adolescente

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Conclusion (1)

Primary amenorrhea can be due to genetic, endocrine, biochemical, anatomical disorders that may have implications for reproductive disturbances in later in life.

Conclusion (2)

1 - The causes leading to the development of adolescent amenorrhea are diverse.

2 – In some complex cases, the adolescent is best managed by a multidisciplinary team : ped. endo., genetists, ped. surgeons, radiologists, psychologists …..

3 – Delay in the evaluation (treatment) of adolescent amenorrhea in some cases may contribute to reduced bone density and other long - term adverse health consequences.

Conclusion (3)

- XY female adolescent are non exceptional conditions

- the cause of XY female adolescent can occur at any point of the male sex differentiation process

- psychological support is necessary

- management depends on the diagnosis

- vaginoplasty should be performed in adolescence

- XY female adolescent should be managed in reference centers / multidisciplany team

Thank you for your attention