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Disorders of Sex Development: An Update

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Is it a girl?
Is it a boy?

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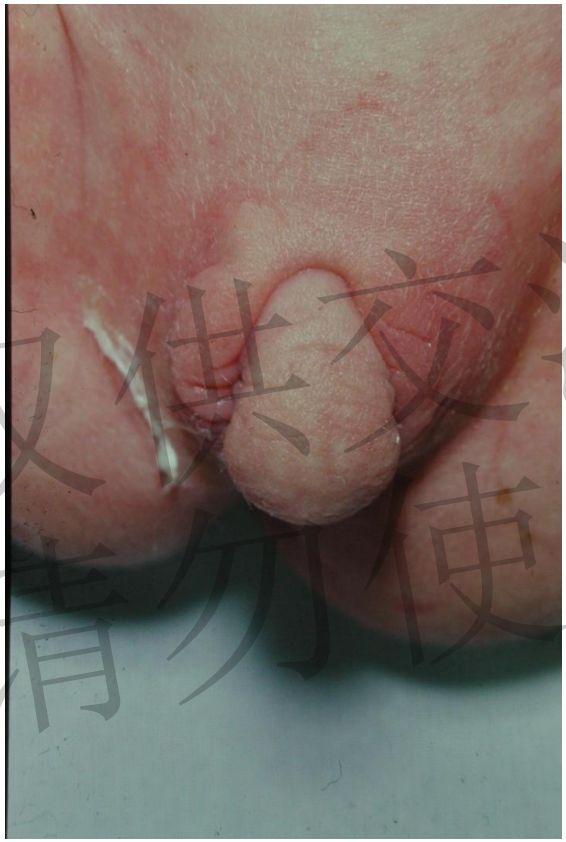
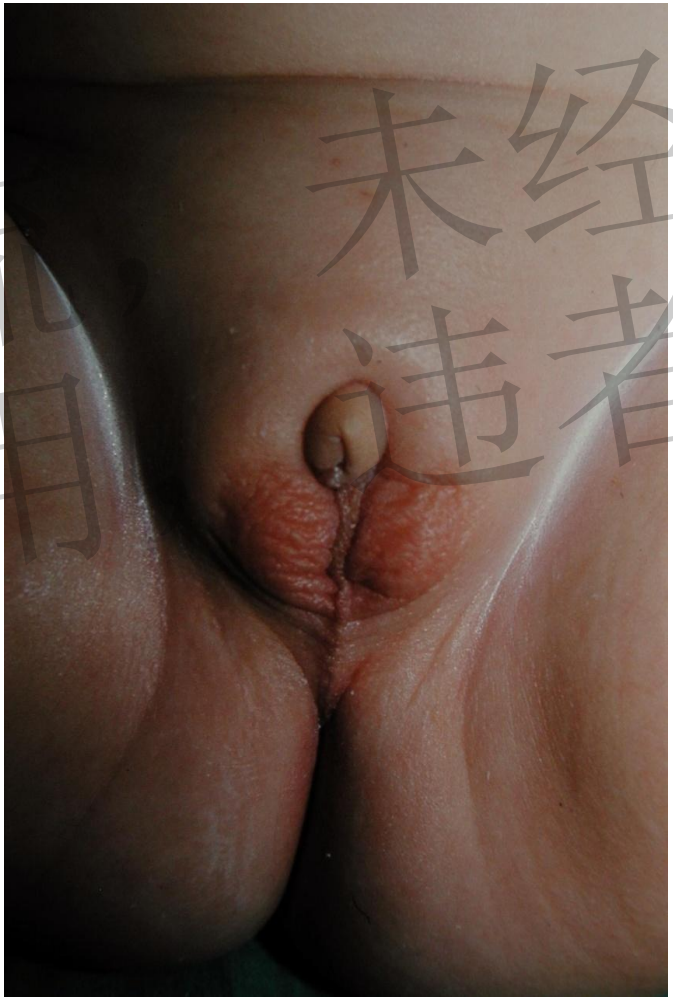
Virilized “female” or undervirilized “male” ?





XX ?

XY ?

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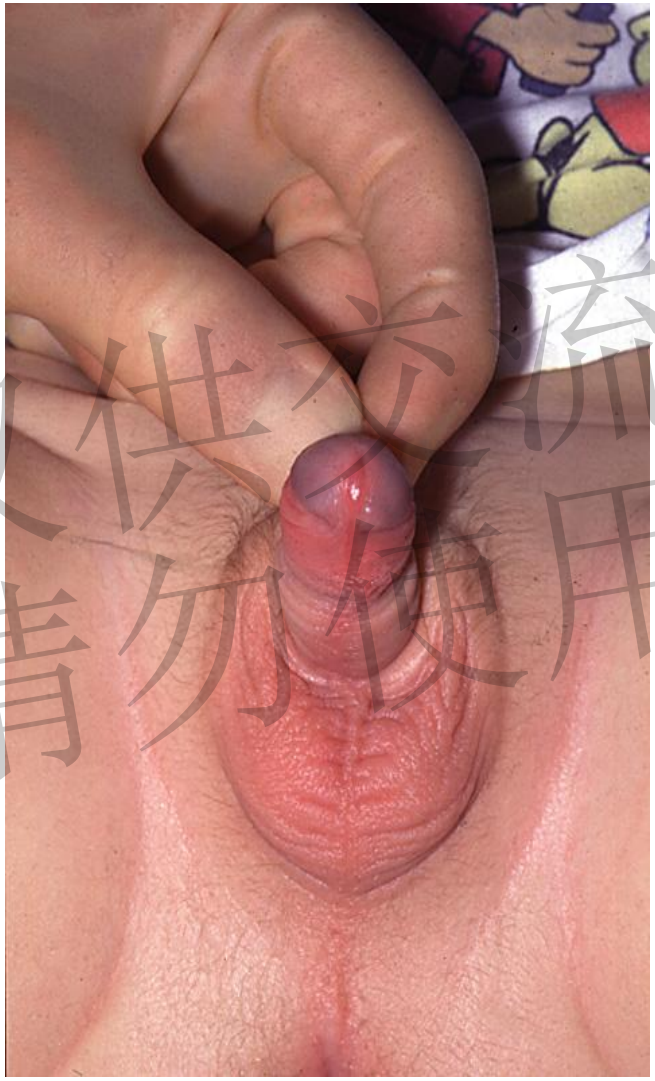
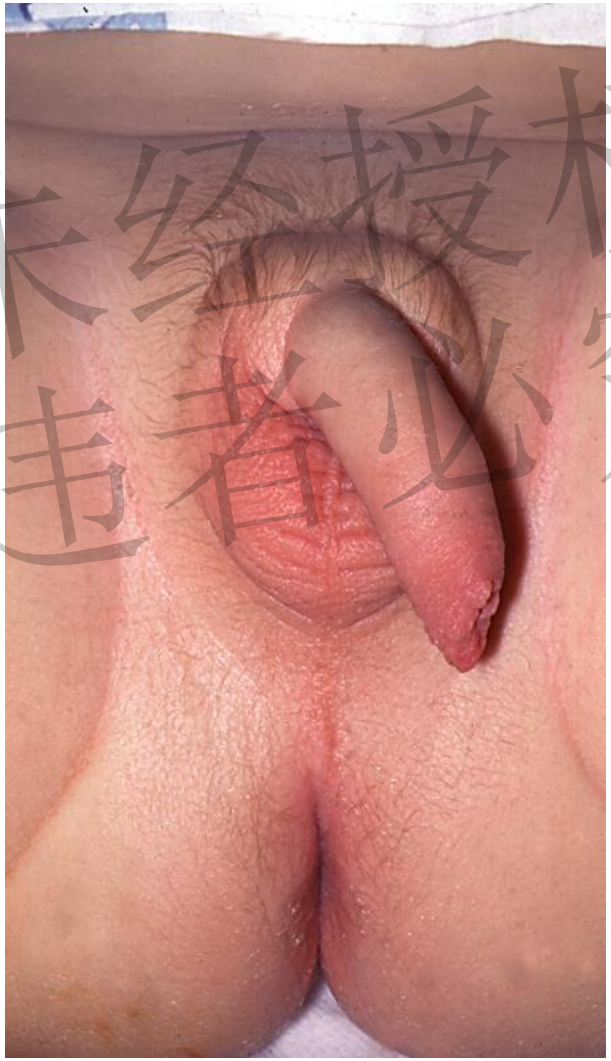
“Complete” sex-reversal





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Overview

- Sex development
- Disorders of Sex Development (Differences in Sex Development)
- Nomenclature
  - Sex chromosome DSD
  - 46,XY DSD
  - 46,XX DSD
- Management
- Genetics

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Sexual differentiation

- To produce males and females with appropriate physical and behavioural characteristics for their respective reproductive roles
- Dependent upon a complex cascade of genetic and biochemical factors

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Sex determination

- Genetic/chromosomal sex
- Gonadal sex
- Phenotypic sex
- Psychological sex
  - Gender identity
  - Gender role
  - Sexual orientation

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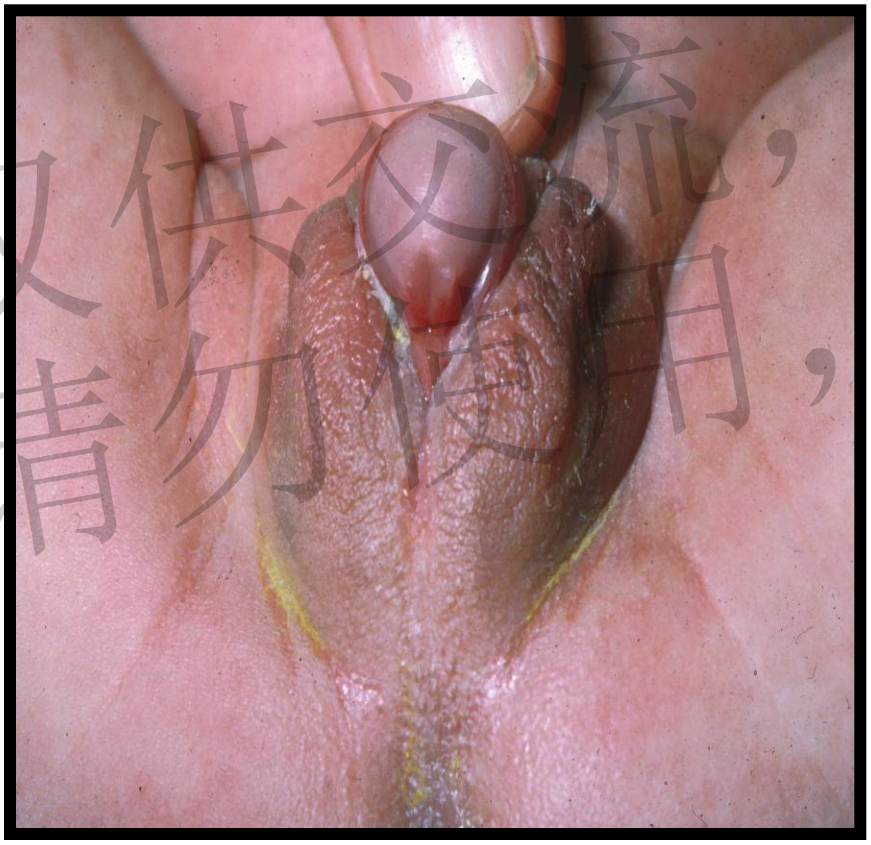
DSD

UCL

Significant genital ambiguity 1: 5-10,000



Diagnosis?
Associations?
Management?
Sex of rearing?
Counselling?
Surgery?
Outcome?

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Presentation	Feature	Examples
Prenatal	Karyotype-phenotype discordance	Many
Neonatal	Atypical genitalia Salt-loss	Many
Childhood	Hernia Androgenization Associated features	CAIS *CYP11B1* Wilms tumor
Puberty	Androgenization	5α reductase *17β HSD III* (*SF-1*) (Ovotestis)
Puberty	Absent puberty	Gonadal dysgenesis 17α hydroxylase
Post-puberty	Amenorrhoea	CAIS
Adult	Infertility ?tumors	CAIS, *SF-1* etc

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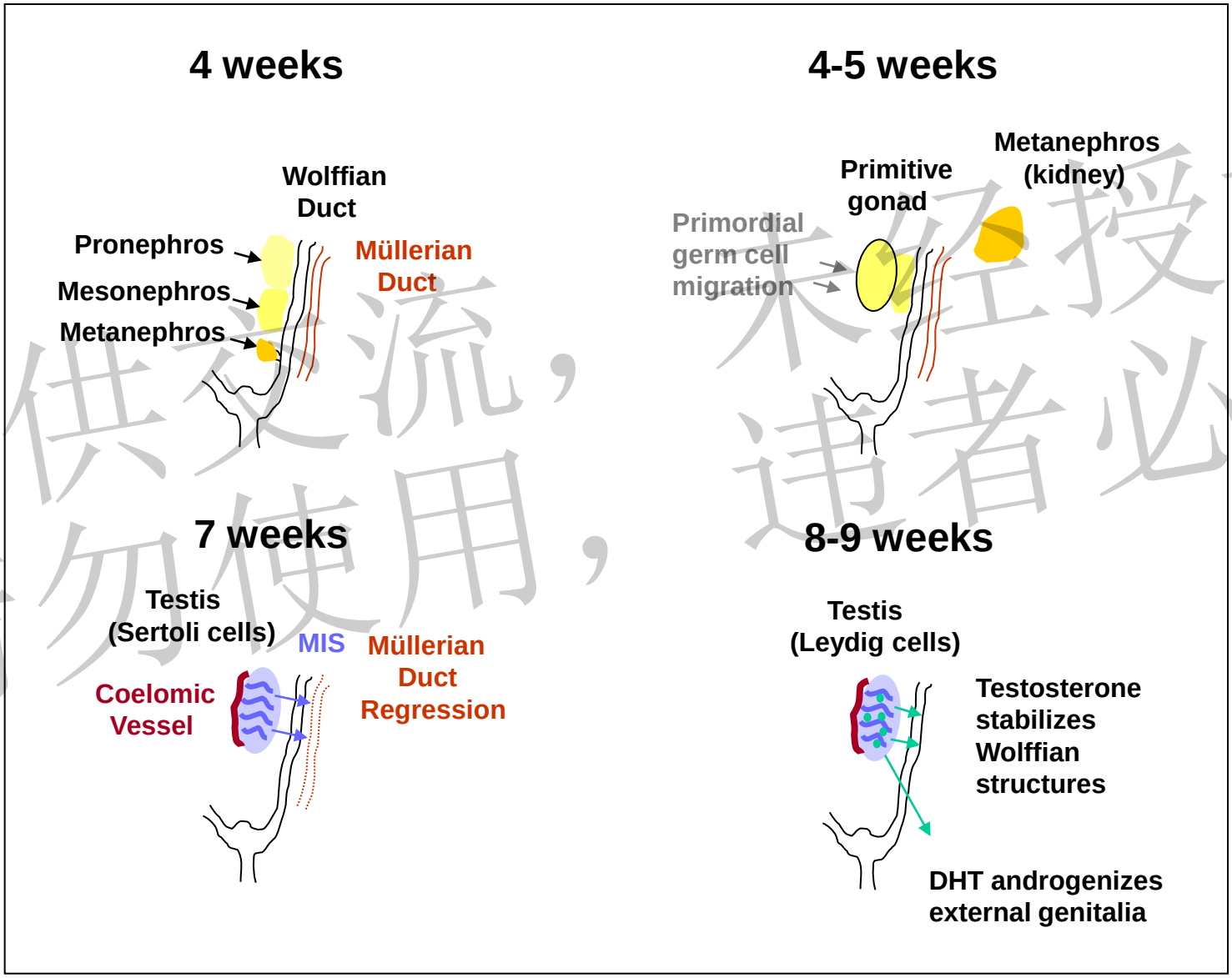
Human Testis Development



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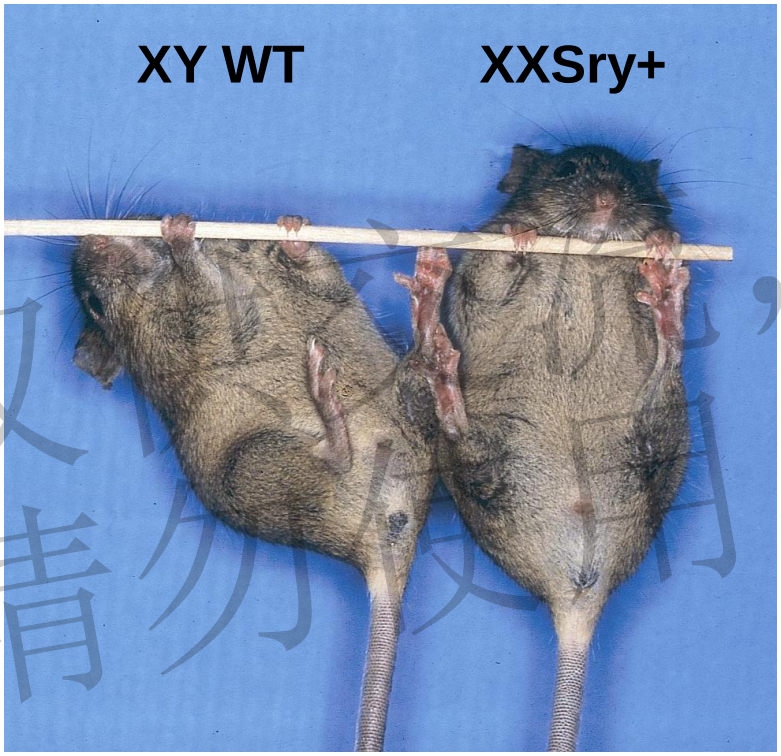
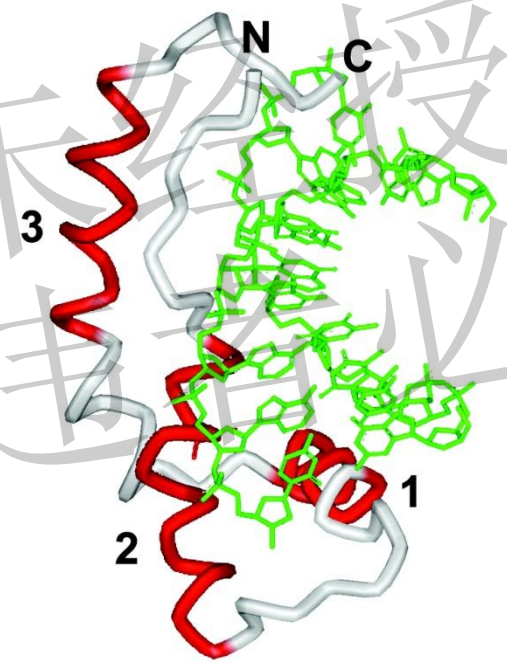
SRY





“testis determining factor”

Courtesy of Robin Lovell-Badge

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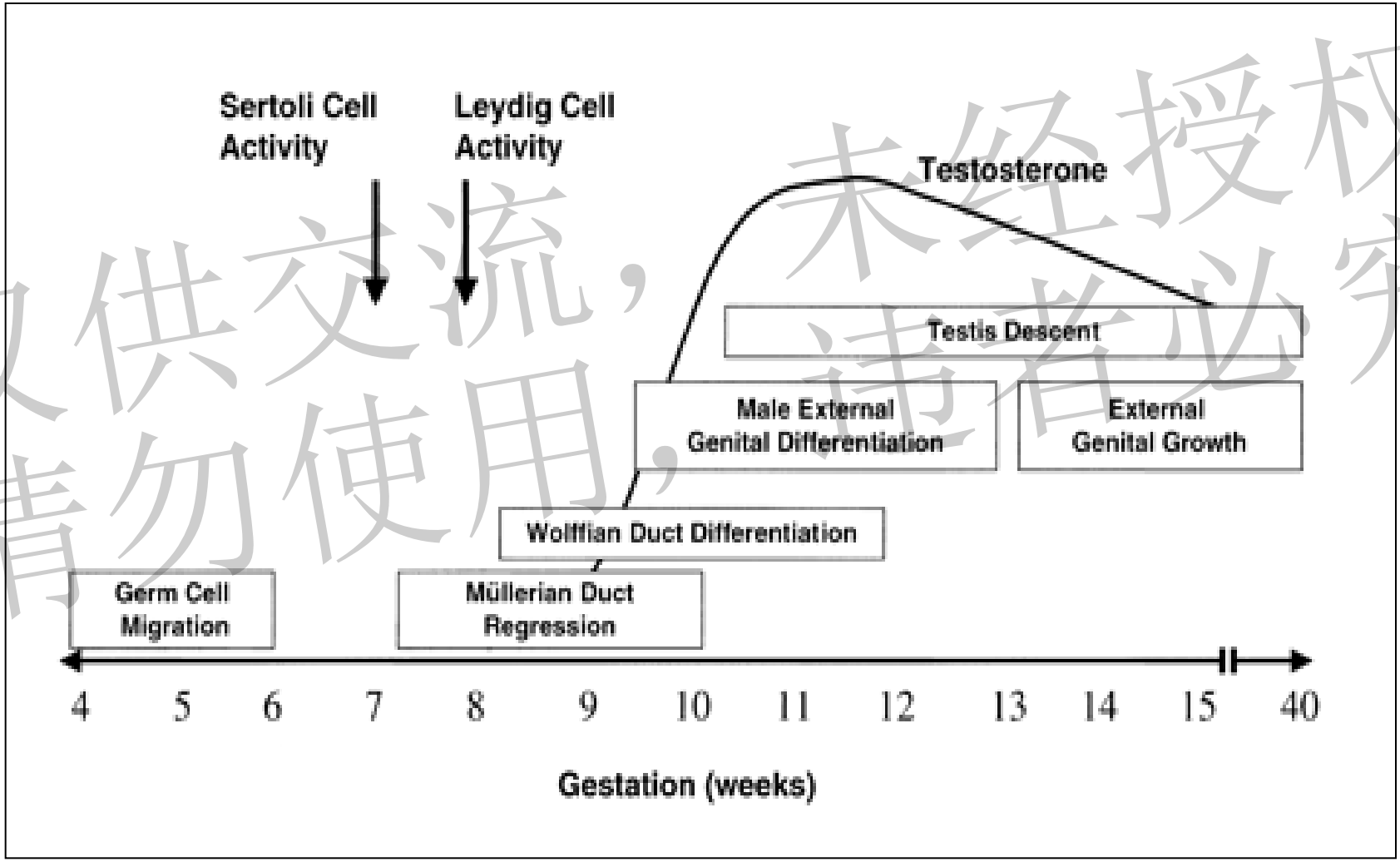
Key events in male sex differentiation



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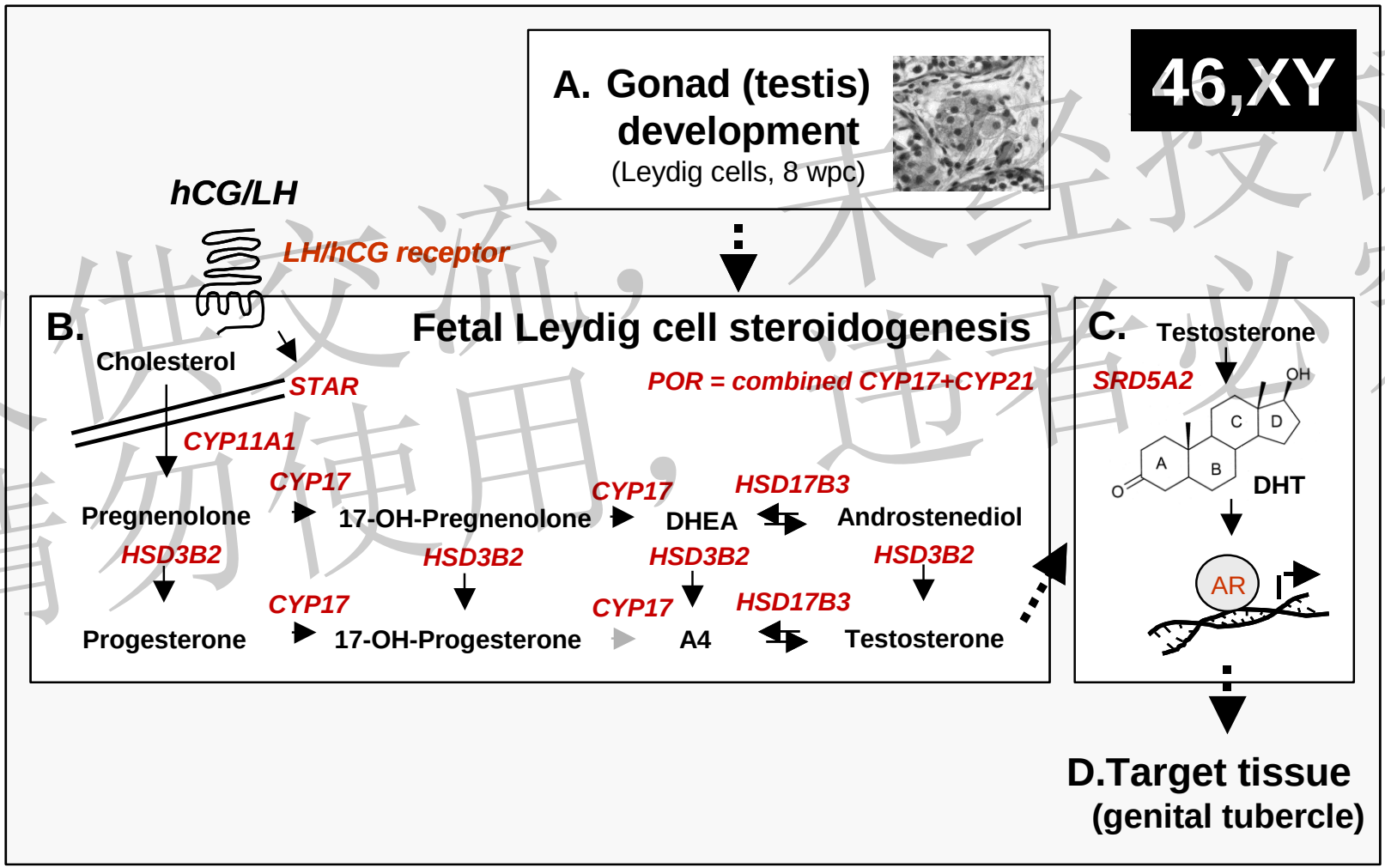
46,XY



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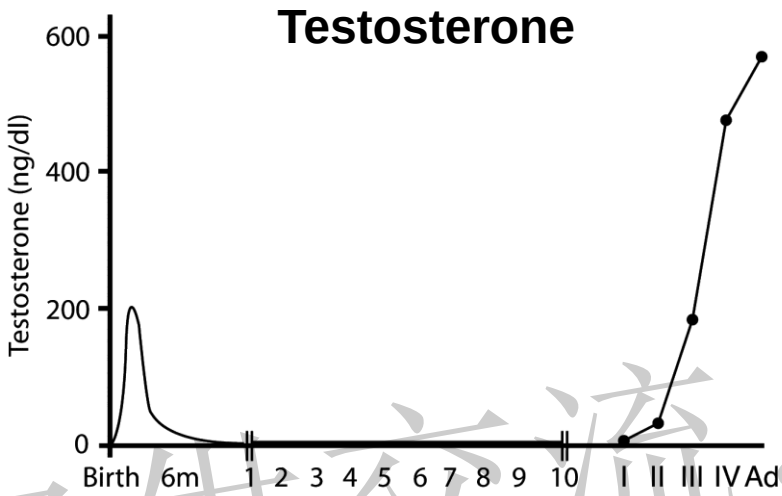

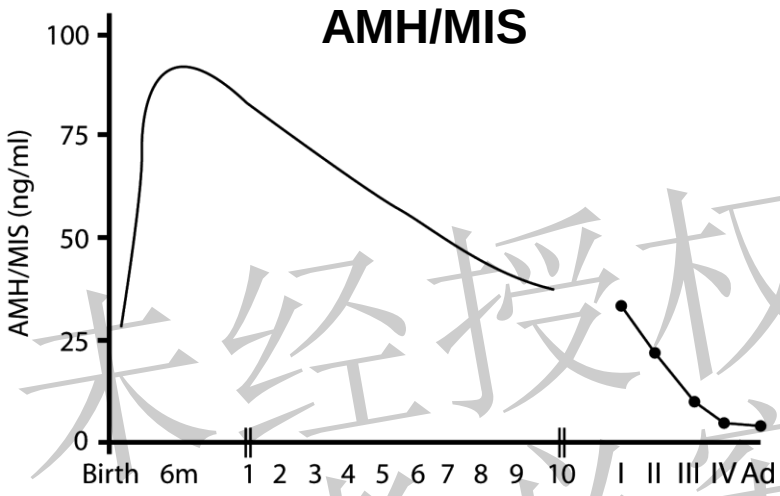

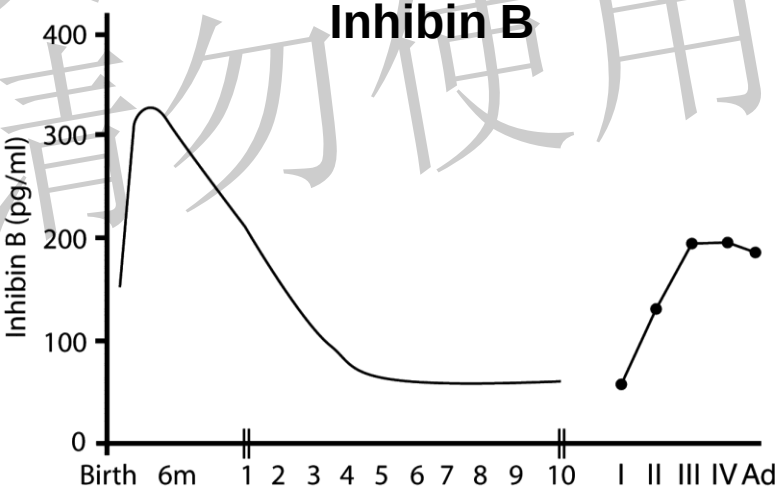

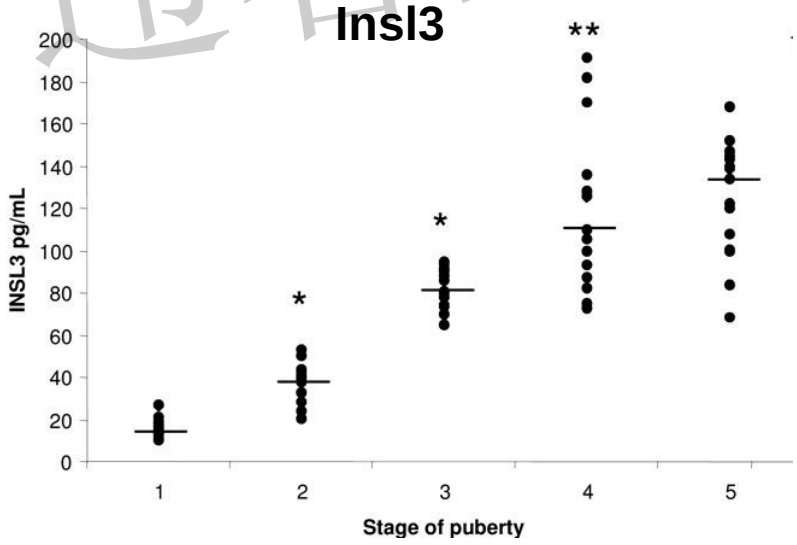

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In the absence of Y chromosome

- Inherent tendency for undifferentiated gonad to develop into an ovary - now thought to be active process
- Ovarian development relatively late
- Germ cells proliferate and form oogonia which then transform into oocytes
- By week 20 granulosa cells envelop oocytes to form primordial follicles - maximal 25 weeks followed by progressive atresia

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Disorders of Sex Development (DSD) (Differences??)

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Consensus statement on management of intersex disorders

I A Hughes, C Houk, S F Ahmed, P A Lee, LWPES1/ESPE2 Consensus Group

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Arch Dis Child 2006

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An updated nomenclature

PREVIOUS	PROPOSED
Intersex	Disorders of sex development (DSD)
Male pseudohermaphrodite Undervirilized XY male Undermasculinized XY male	46,XY DSD
Female pseudohermaphrodite Overvirilized XY male Overmasculinized XY male	46,XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46, XX testicular DSD
XY sex reversal	46, XY complete gonadal dysgenesis

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Classification

Sex Chromosome DSD	46,XY DSD	46,XX DSD
a) 45,X Turner & variants	a) Disorders of gonadal (testicular) development	a) Disorders of gonadal (ovarian) development
b) 47,XXY Klinefelter & variants	b) Disorders of androgen synthesis & action	b) Androgen excess
c) 45,X/46,XY mixed gonadal dysgenesis	c) Others	c) Others
d) 46,XX/46,XY chimerism		

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Sex Chromosome DSD	46,XY DSD	46,XX DSD
A: 47,XXY (Klinefelter Syndrome & variants) **B: 45,X (Turner Syndrome & variants)** **C: 45,X/46,XY mosaicism (mixed gonadal dysgenesis)** **D: 46,XX/46,XY (chimerism/mosaicism)**	**A: Disorders of testis development** 1. Complete or partial gonadal dysgenesis (e.g. *SRY*, *SOX9*, *SF1*, *WT1*, *DHH*, *MAP3K1*, *GATA4 etc*) 2. Impaired fetal Leydig cell function (e.g. *SF1/NR5A1*, *CXorf6/MAMLD1*) 2. Ovotesticular DSD 3. Testis regression	**A: Disorders of ovary development** 1. Gonadal dysgenesis 2. Ovotesticular DSD 3. Testicular DSD (eg *SRY+*, *dup SOX9, RSPO1; disruption of SOX3 or SOX9 promoter*)
	B: Disorders in androgen synthesis or action 1. Disorders of androgen biosynthesis LH receptor mutations Smith-Lemli-Opitz syndrome Steroidogenic acute regulatory protein Cholesterol side chain cleavage 3β-hydroxysteroid dehydrogenase II 17α-hydroxylase/17,20-lyase P450 oxidoreductase Cytochrome b5 17β-hydroxysteroid dehydrogenase III 5α-reductase II AKR1C2 (AKR1C4) 2. Disorders of androgen action Androgen Insensitivity Syndrome Drugs & environmental modulators	**B: Androgen excess** 1. Fetal 3β-hydroxysteroid dehydrogenase II 21-hydroxylase P450 oxidoreductase 11β-hydroxylase Glucocorticoid receptor mutations 2. Fetoplacental Aromatase deficiency ?Oxidoreductase deficiency 3. Maternal Maternal virilizing tumours (e.g., luteomas) Androgenic drugs
	C: Other 1. Syndromic associations of male genital development (50+) (e.g. cloacal anomalies, Robinow, Aarskog, Hand-Foot-Genital, popliteal pterygiumetc) 2. Persistent Müllerian duct syndrome 3. Vanishing testis syndrome 4. Isolated hypospadias 5. Congenital hypogonadotropic hypogonadism 6. Cryptorchidism 7. Environmental influences	**C: Other** 1. Syndromic associations (e.g. cloacal anomalies) 2. Müllerian agenesis/hypoplasia (e.g., MURCS) 3. Uterine abnormalities (e.g., MODY5) 4. Vaginal atresis (e.g., McKusick-Kaufman) 5. Labial adhesions

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46XY Disorders of Sex Development (DSD)

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Bipotential gonad

WT1^KTS
SF1
CBX2
MAP3K1
GATA4/FOG2

↓

Testis

SRY
SOX9
DMRT1/2
DHH
ATRX
ARX
TSPYL1
MAMLD1

↓ ↓

Sertoli | **Leydig**

↓ *steroidogenesis*

AMH
MISRII
SOX9
SF1

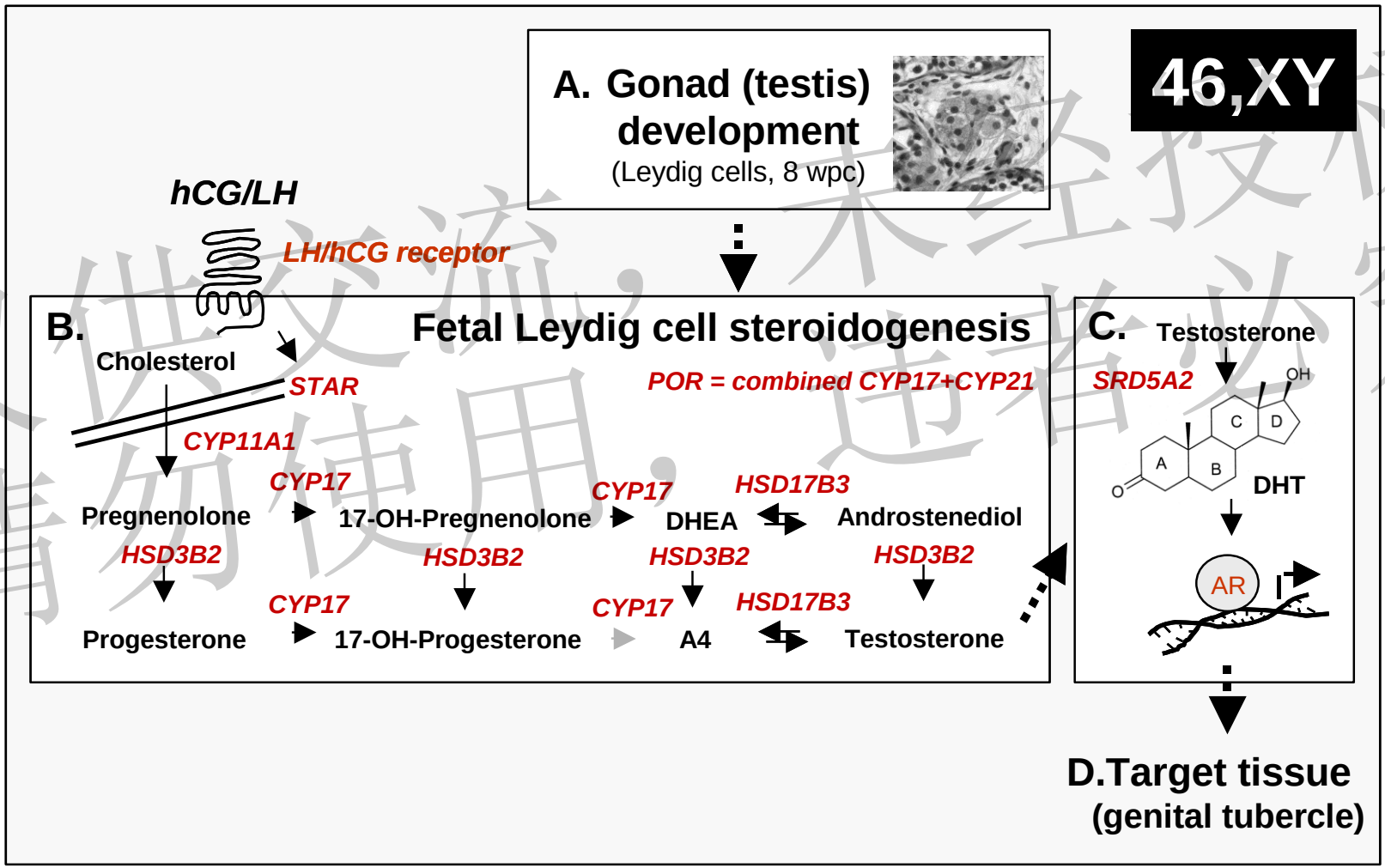
LHCGR
CYP11A1
STAR
CYP17A1
POR/Cyb5
3βHSD2
17βHSD3
SRD5A2
AR
Targets

INSL3
LGR8

↓

Müllerian Regression | **Phallic growth** | **Testis Descent**

46,XY



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The under-virilised male (46XY DSD)

Gene	Function	Associations
WT1	Loss	WAGR (deletions) Denys-Drash (renal) Frasier syndrome (renal)
SF-1	Loss	Adrenal failure, uterus
Sry	Loss	-
SOX9	Loss	Campomelic dysplasia
DAX-1	Gain (duplication)	-
WNT4	Gain (duplication)	-

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The under-virilised male (46XY DSD)

Gene	Function	Associations
LHR	Loss	-
StAR	Loss	Adrenal failure
CYP11A1	Loss	Adrenal failure
HSD3B2	Loss	Adrenal failure
CYP17	Loss	↓cortisol, ↑BP, ↑aldosterone
HSD17B3	Loss	↑androstenedione, virilise at puberty
5α reductase	Loss	↑T:DHT ratio, virilize at puberty
Androgen Receptor	Loss	↑testosterone

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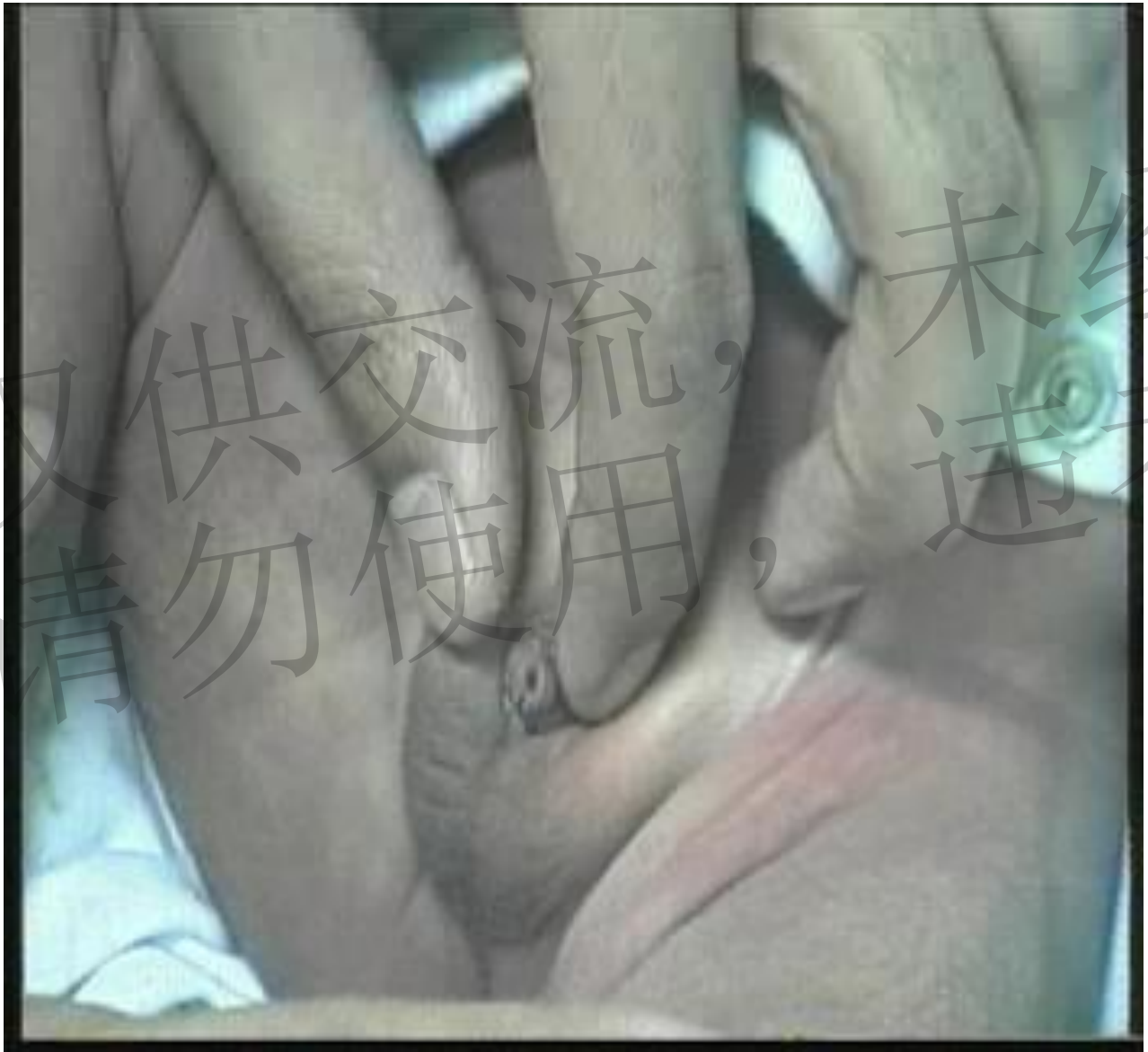
Case 1: Micropenis (d17)



46 XY

Consanguineous pedigree

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Initial investigations (d17)

LHRH test

Time (mins)	0’	20’	60’
LH (iU/L)	23.5	38	37.2
FSH (iU/L)	2.4	3.0	3.6

Synacthen test

Time (mins)	0’	30’	60’
Cortisol (nmol/l)	<28	155	203
17-OHP (nmol/l)	8.2	5.3	-

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Initial investigations (d17-38)

3 day/week hCG test

	Basal	3d	3w
DHEAS (μmol/l)	<0.81	<0.81	<0.81
Androstenedione (mmol/l)	<1.0	<1.0	2.8
Testosterone (nmol/l)	2.6	3.4	3.3
Dihydrotestosterone (nmol/l)	0.61	1.07	0.89

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Adrenal investigations (1 month)

Cortisol profile

Clock time	16h	20h	24h	4h	8h
Cortisol (nmol/l)	53	<28	90	125	39

Repeat synacthen test

Time (mins)	0’	30’	60’
Cortisol (nmol/l)	43	198	235

ACTH 96.1/113 ng/l (10-50)
Na 136 mmol/l (138-145), K 5.3 mmol/l (3.5-5.5)
Progesterone 12.4 nmol/l (0.4-5.0)
Aldosterone 5229 pmol/l (1000-3800)
Renin 3.6 pmol/ml/h (<25)

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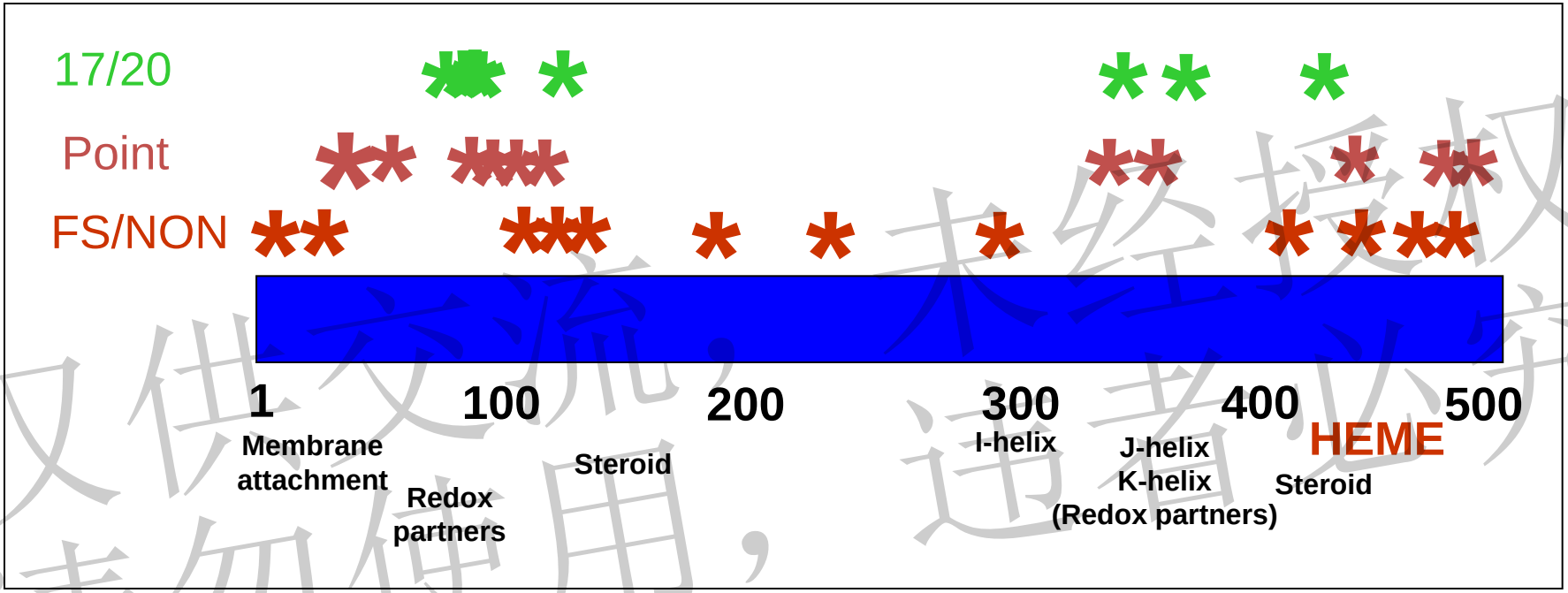
17α-hydroxylase/17,20-lyase deficiency



- Phenotypic females (46,XX; 46,XY) or ambiguous genitalia (46,XY)
- Hypertension/hypokalaemia
- Failure of pubertal development (46,XX; 46 XY)

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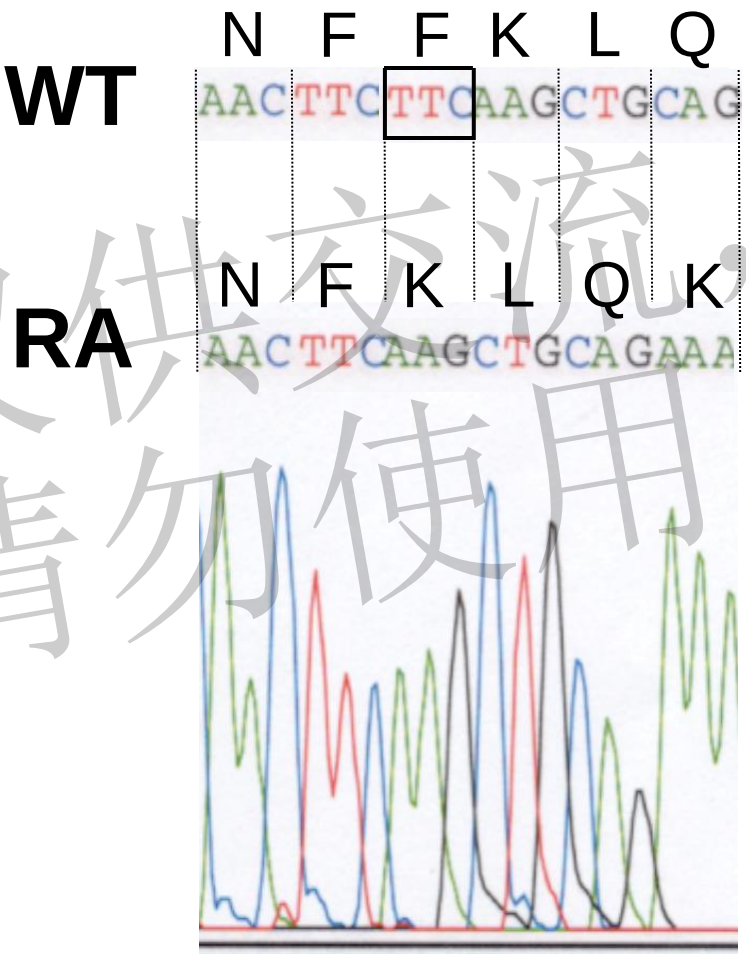
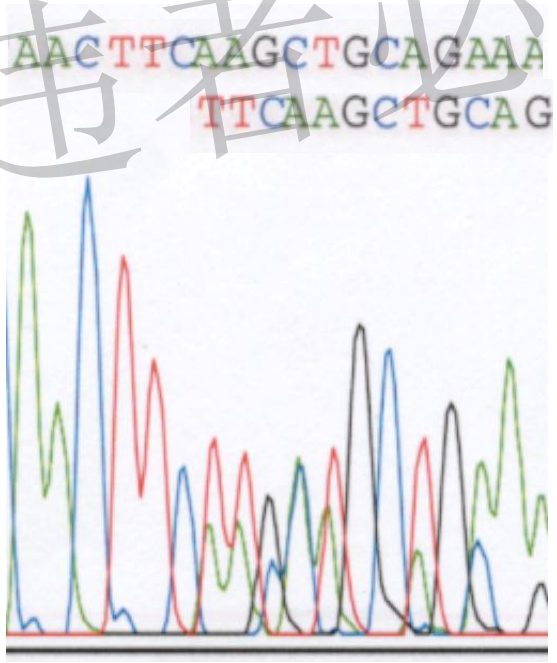
Baby RA: Phe54 deletion in CYP17



Parents (heterozygous)



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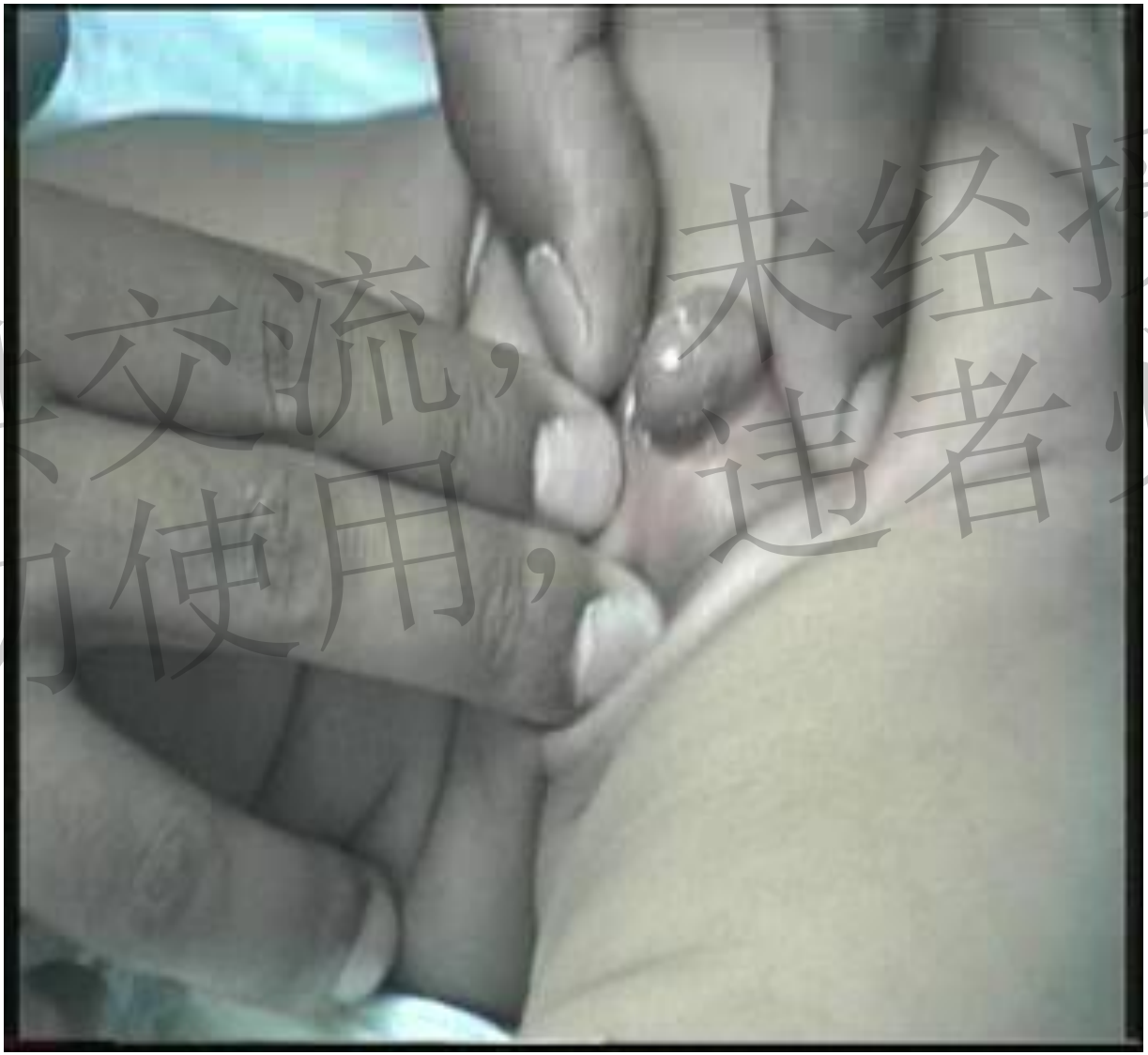
Post-testosterone (5 months)



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Case 2 – Clinical History

- Born 40+6/40, SVD, 3.45kg
- Thought to be a girl at delivery
- Clitoral enlargement noticed
- “testes” palpated
- Mild respiratory distress
- O/E: 1 cm phallus with hypospadias, bilateral gonads palpable, pigmented labioscrotal folds

- Karyotype: 46,XY (FISH)
- USS – bilateral gonads, no uterus

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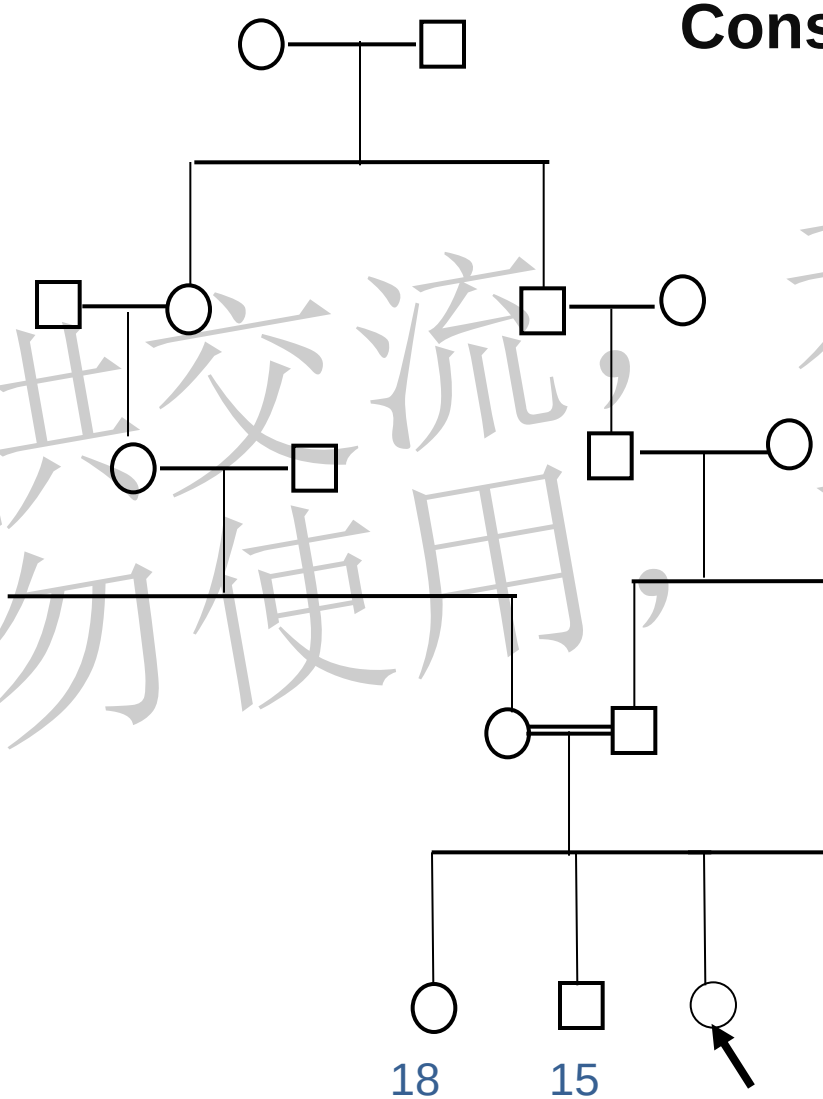
Case 2: Family History



Consanguineous Fijian family

Father – Army
Mother – Dental nurse
(Great grandparents are sisters)
In UK for 3 years
Uncle - Pastor
Prayed for girl in pregnancy
"Planned family"

Sister
"infertile"

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Case 2 – Investigations

- **Testosterone 1.4 nmol/L, LH <0.7 IU/L, FSH 1.9 IU/L**
- **Normal cortisol secretion**
- **3 day HCG test: peak testosterone 1.5 nmol/L, A4 1.4 nmol/L**

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Case 2 – SOR

- Convinced baby is a girl
- Fertility & Behaviour “not an issue”
- Would have tests, but sure their baby is a girl, and felt that the genital appearance supports their belief
- Cystoscopy and EUA
  - Normal urethra, bladder and ureteric orifices
  - Second channel identified approximately 1cm distal to the bladder neck and vagina was identified
  - Length of vagina 2.1cm, quite distance from the urethral meatus
- Gonadectomy done at the same setting

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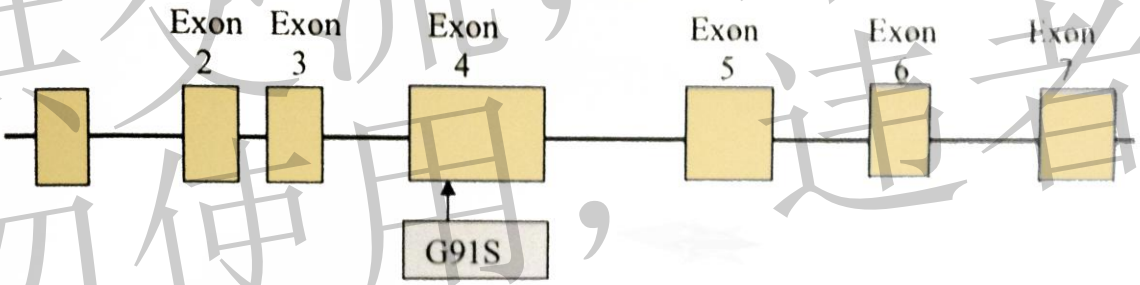
Case 2: Genetic analysis

- **Heterozygous *NR5A1* mutation - in the A-box region of SF1 which affects DNA-binding and gene transactivation**



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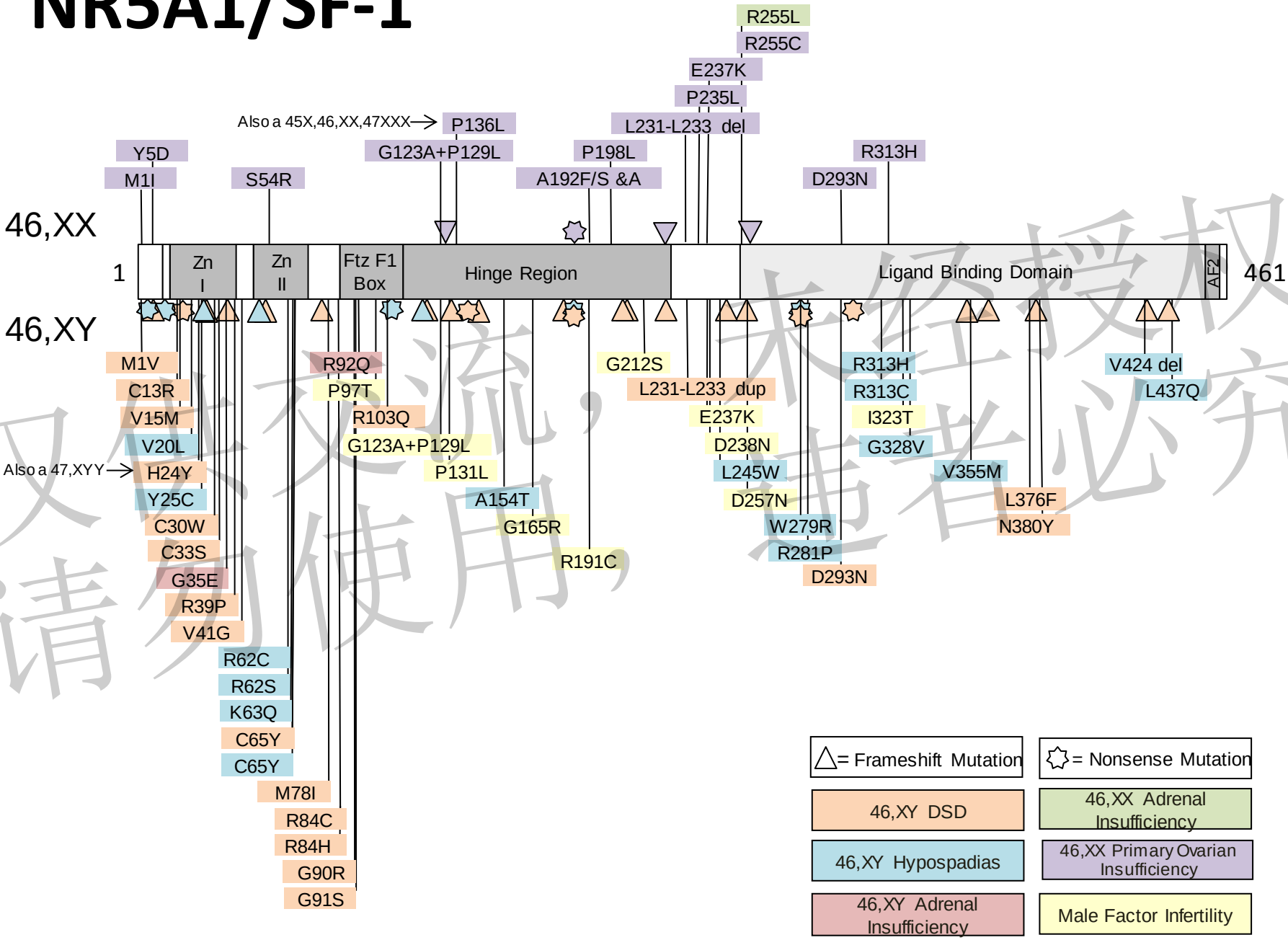
- **Diagnosis explained: Adrenal function normal at the moment but monitored regularly**
- **Mutation inherited from mother – normal ovarian function**

NR5A1/SF-1



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Case 2 – issues

- Age 7 years
- ?Enlarging clitoris – no objective evidence
- ?Gender Identity Disorder (GID)
- Plan to induce puberty aged 10.5 – 11 years
- Identified herself as male gender and preferred to stand up during urination (4Y)
- Continues to be boyish
- Prefers to dress up like a boy
- Wants to bathe with brothers
- Normal adrenal function, undetectable androgens and Inhibin B
- ONGOING PSYCHOLOGICAL ASSESSMENT

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The virilised female (46 XX DSD)

Gene	Function	Associations
Sry	Gain (translocation)	-
SOX9	Gain (duplication)	-
WNT4	Loss (mutation)	-
CYP21A2	Loss	↓ cortisol, salt loss, ↑17OHP
CYP11B1	Loss	↓ cortisol, ↑ BP, ↑ DOC
HSD3B2	Loss	↓ cortisol, salt loss, ↑DHEA (mild virilization)
CYP19	Loss	↓ oestradiol, ↑testosterone, maternal virilization

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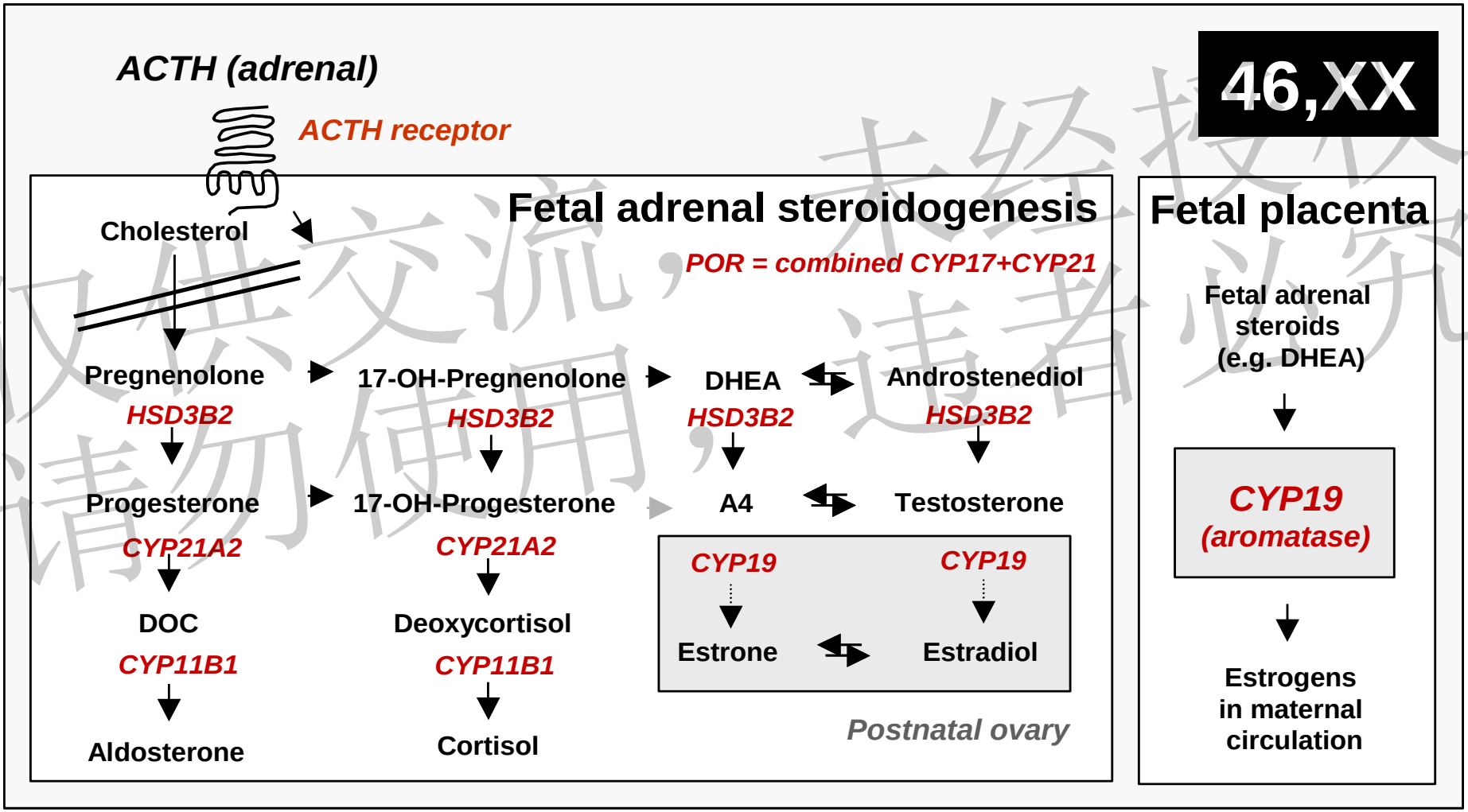
46,XX



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Pedigree 1

- 46,XX; clitoromegaly
- Raised female
- Elevated FSH, LH
- Elevated testosterone
- Detectable oestradiol
- Cystic ovaries
- Breast development (stage 2)

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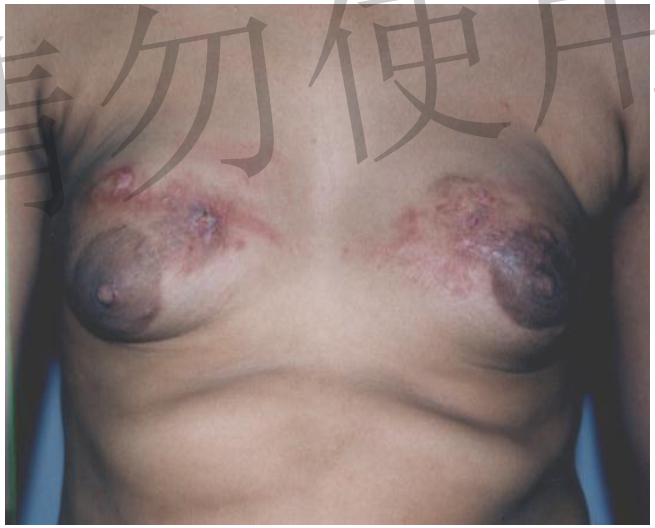
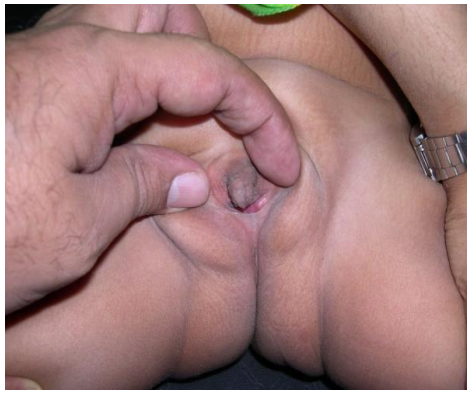
Pedigree 2

Prader III, 46,XX
Male SOR
“Male” identity



Prader III, 46 XX



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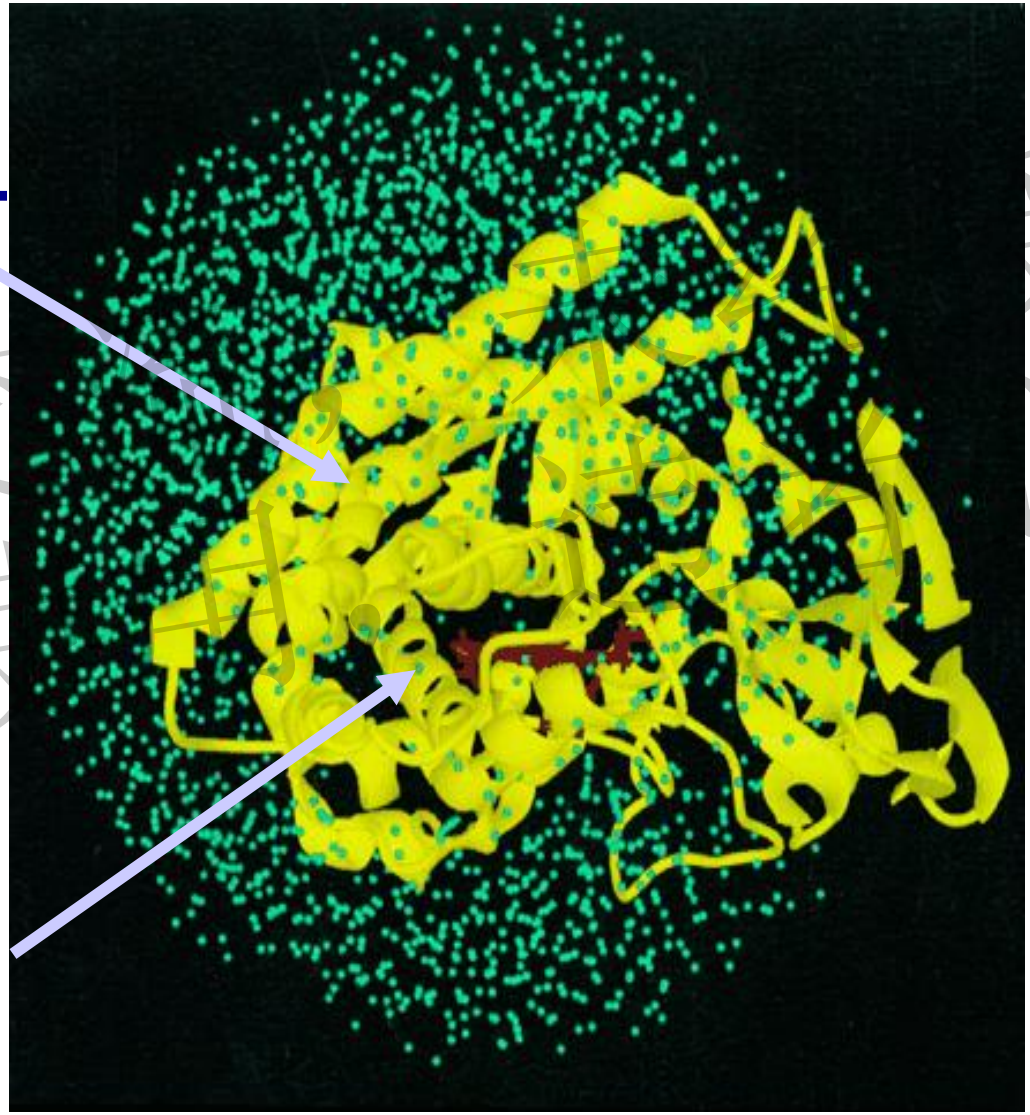
Partial aromatase deficiency



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Why make a diagnosis?

- Adrenal risk
- Associated features
- Sex assignment
  - Likely gender identity
  - Urological function
  - Sexual function
  - Fertility options
  - Treatment options
- Tumour risk
- Counseling family

Resolution

Benefits *versus* Burdens

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Management

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First and foremost.....

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DELAY REGISTRATION IF NECESSARY

The first hours/days

- **B**onding
- **A**drenal
- **S**ex-assignment
- **I**maging
- **C**ytogenetics

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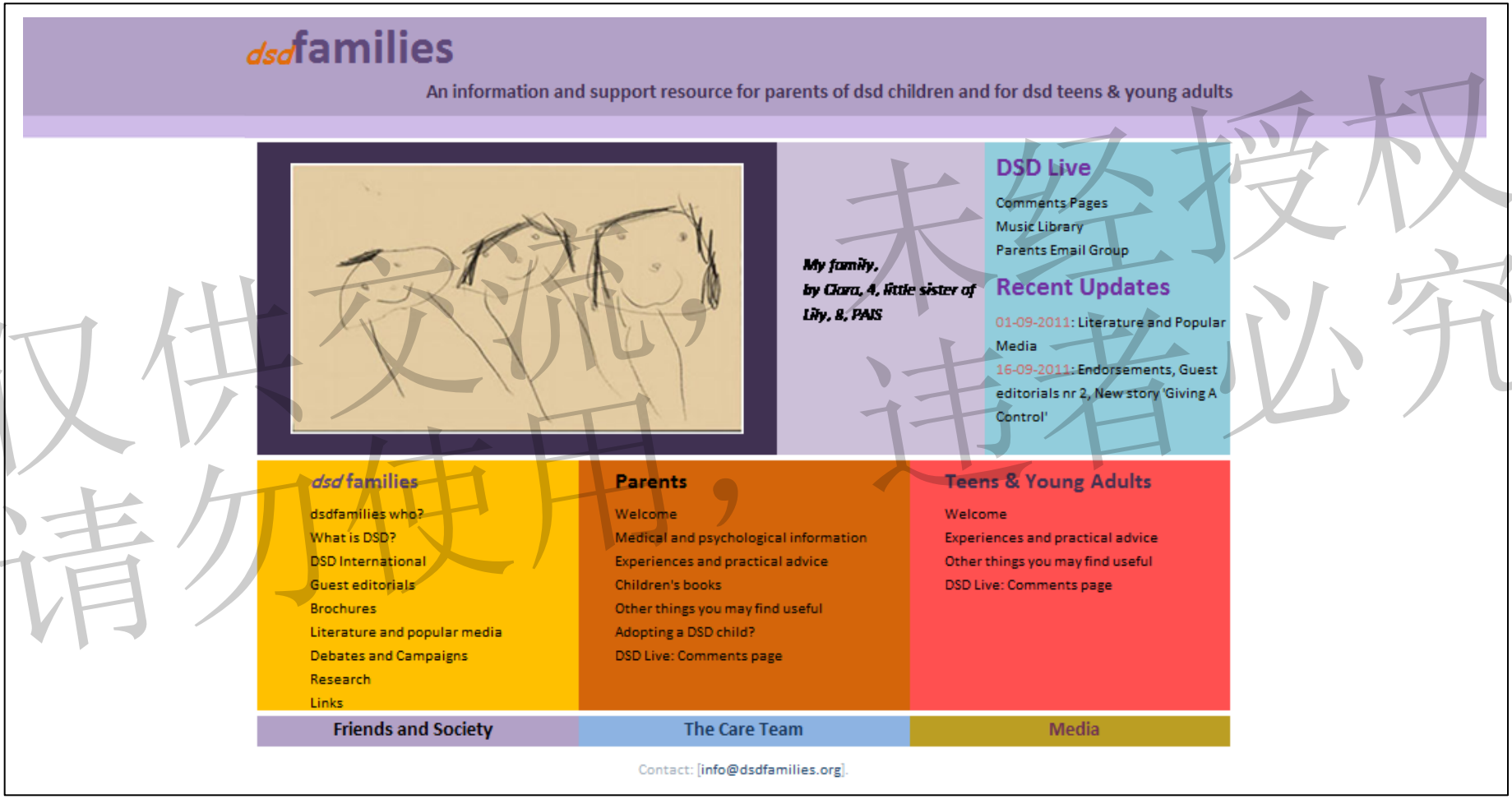
Information & support



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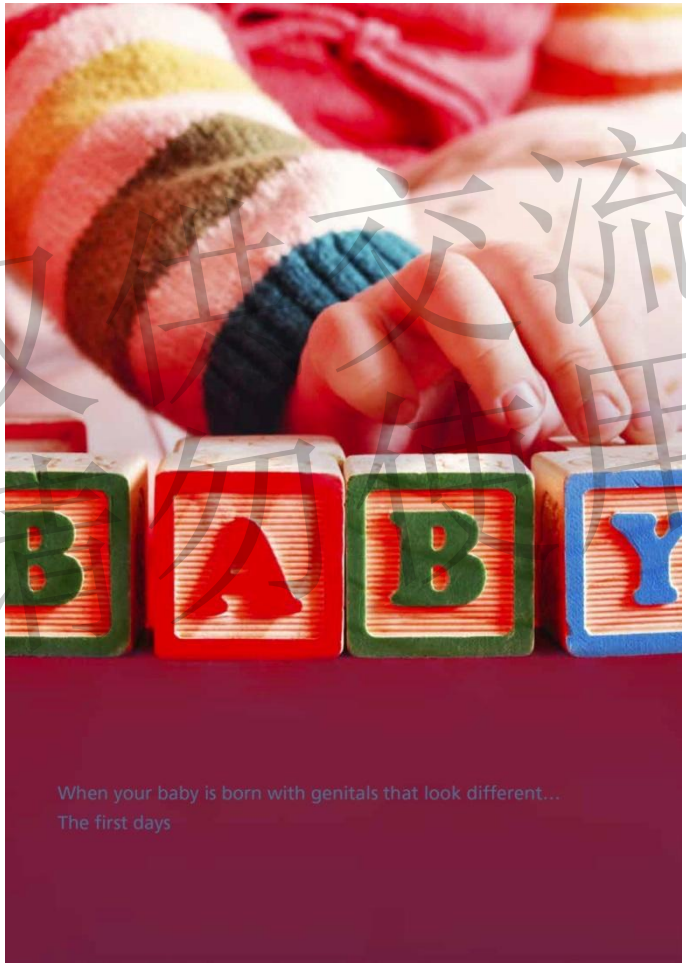
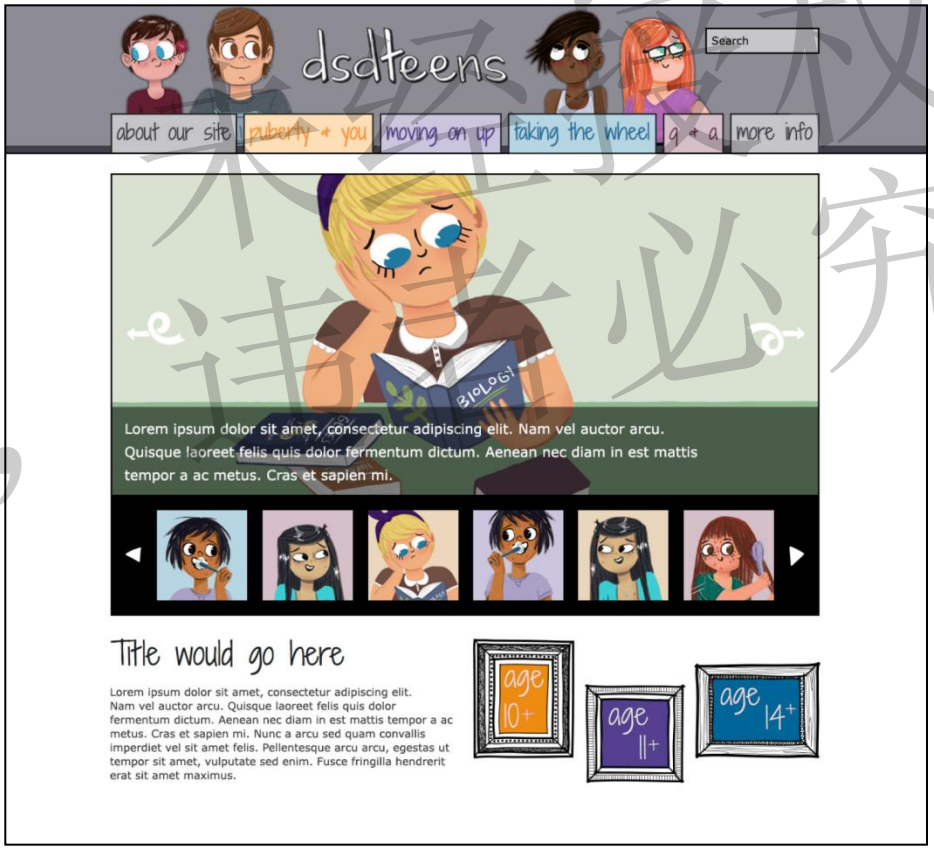
dsdfamilies.org

Engagement

Information



Websites



Support Groups

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Management of DSD: Sex of Rearing

- Decided on completion of investigations (possibly weeks)
- Decision made by multidisciplinary team with parental input; several discussions, avoid gender reassignment in future
- Based upon:
  - Results of tests – diagnosis, potential testicular function
  - Prenatal androgen exposure
  - Prospects of fertility
  - Presence of uterus
  - Future sexual function – size of penis and potential to grow
  - Parental and clinical views
  - Cultural influence
- In CAH diagnosed at birth, sex of rearing more straightforward

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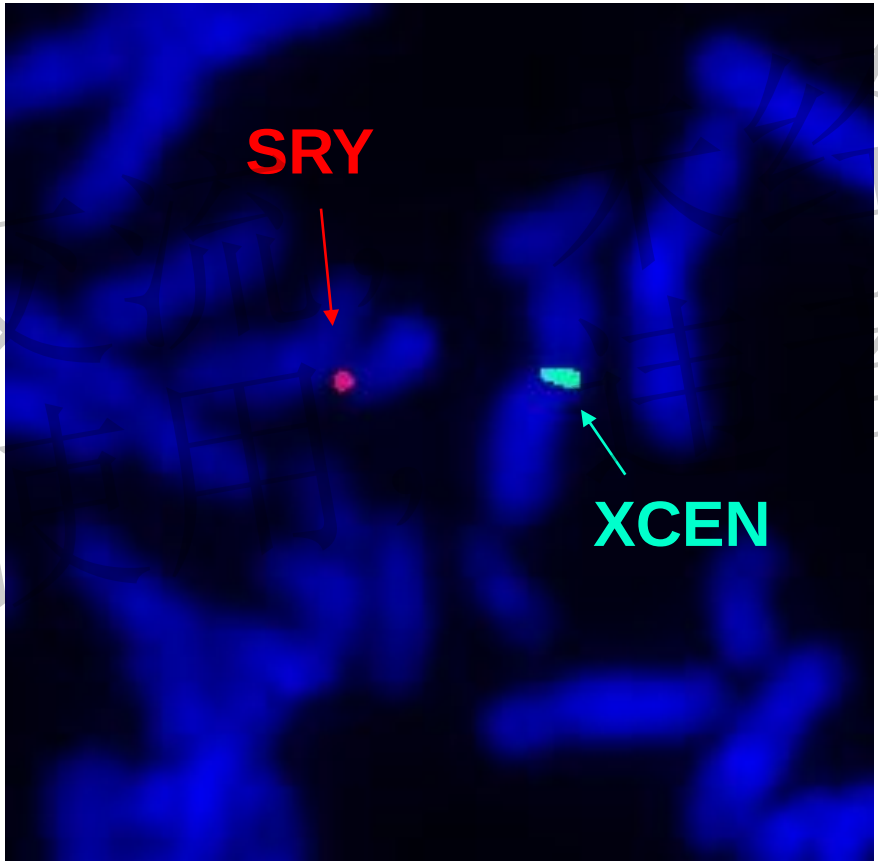
FISH



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History & Exam

History

- Drugs
- Maternal
- Family
  - Stillbirths
  - Miscarriages
  - Deaths
  - Fertility issues
- Consanguinity
- Birth

Examination

- Hyperpigmentation
- Dysmorphic/syndrome
- Associated features
- Genital examination
  - phallic size
  - fat
  - corporal consistency
  - chordee
  - scrotal rugosity
  - gonads – size, position
  - anus
- External masculinization score (EMS)
  - gonads
  - phallus
  - site of urethral meatus
  - labioscrotal fold fusion

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Investigations

First line

FISH (SRY); U&E; glucose; 17OHP; cortisol; urinalysis; LH/FSH/testosterone; USS

Then…

Adrenal: ACTH, pregnenolone, progesterone, 17OH-pregnenolone, 11-deoxycortisol, DHEAS
Plasma renin activity, aldosterone, DOC
Synacthen stimulation tests; 7DHC

Testis: DHEAS, androstenedione, testosterone, DHT; AMH, inhibin B
hCG stimulation tests (3 day, 3 week)
LHRH stimulation test

Urine steroid analysis by GC-MS,

Imaging: MRI, cystourethroscopy, sinogram/genitogram

Surgical: Laparoscopy, gonadal biopsy and histology, cytogenetics & molecular analysis

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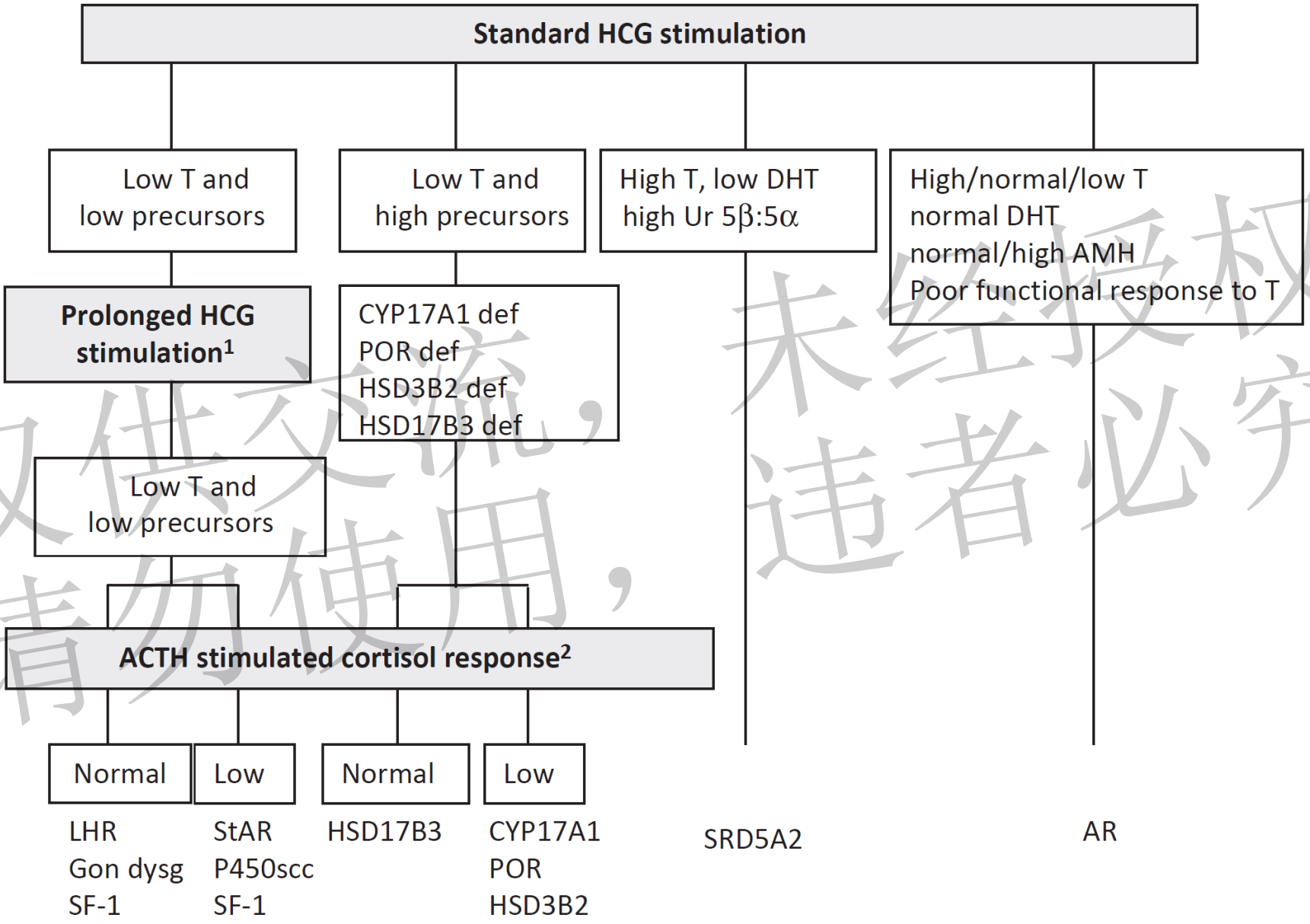

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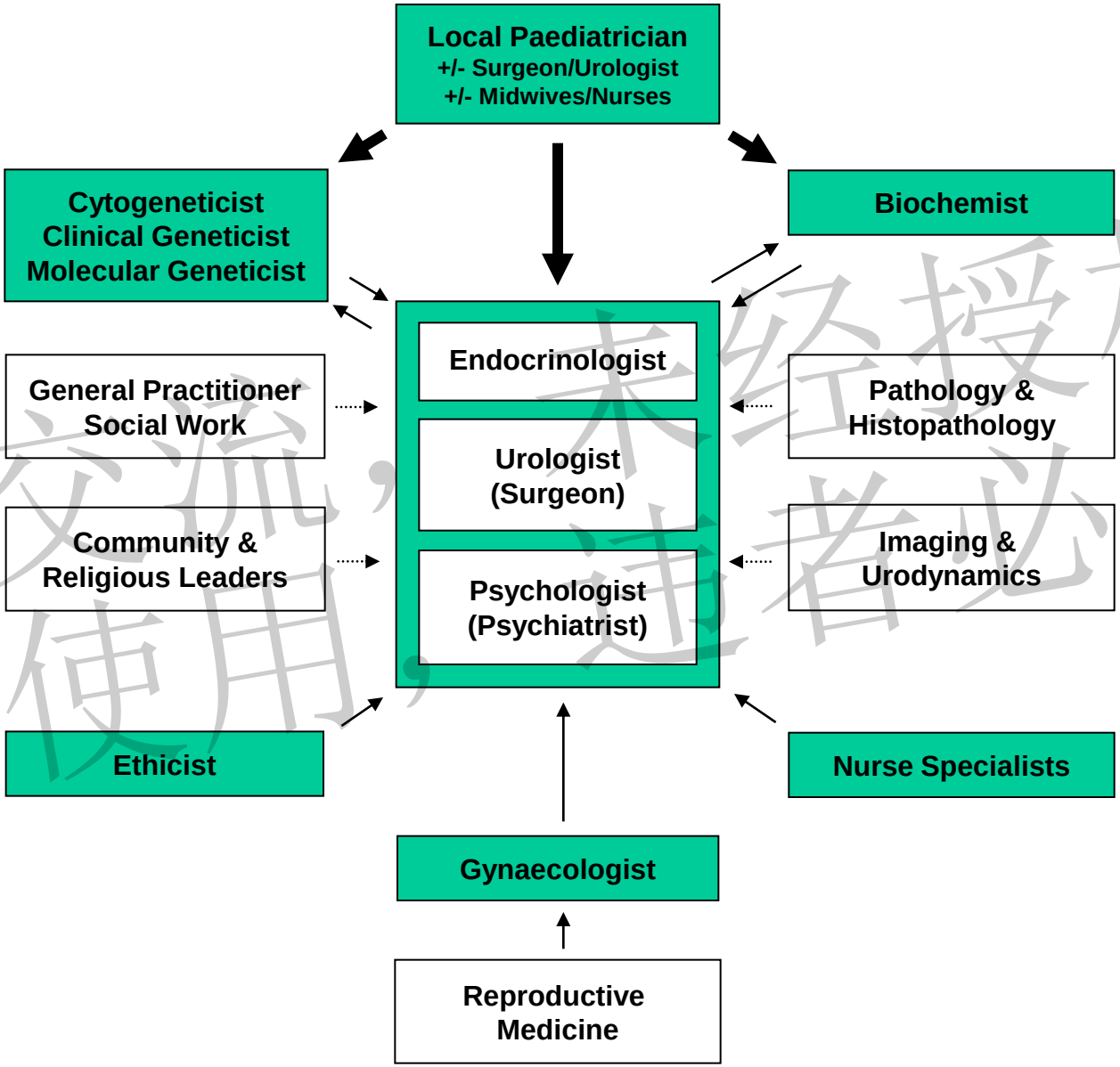
Multidisciplinary Team



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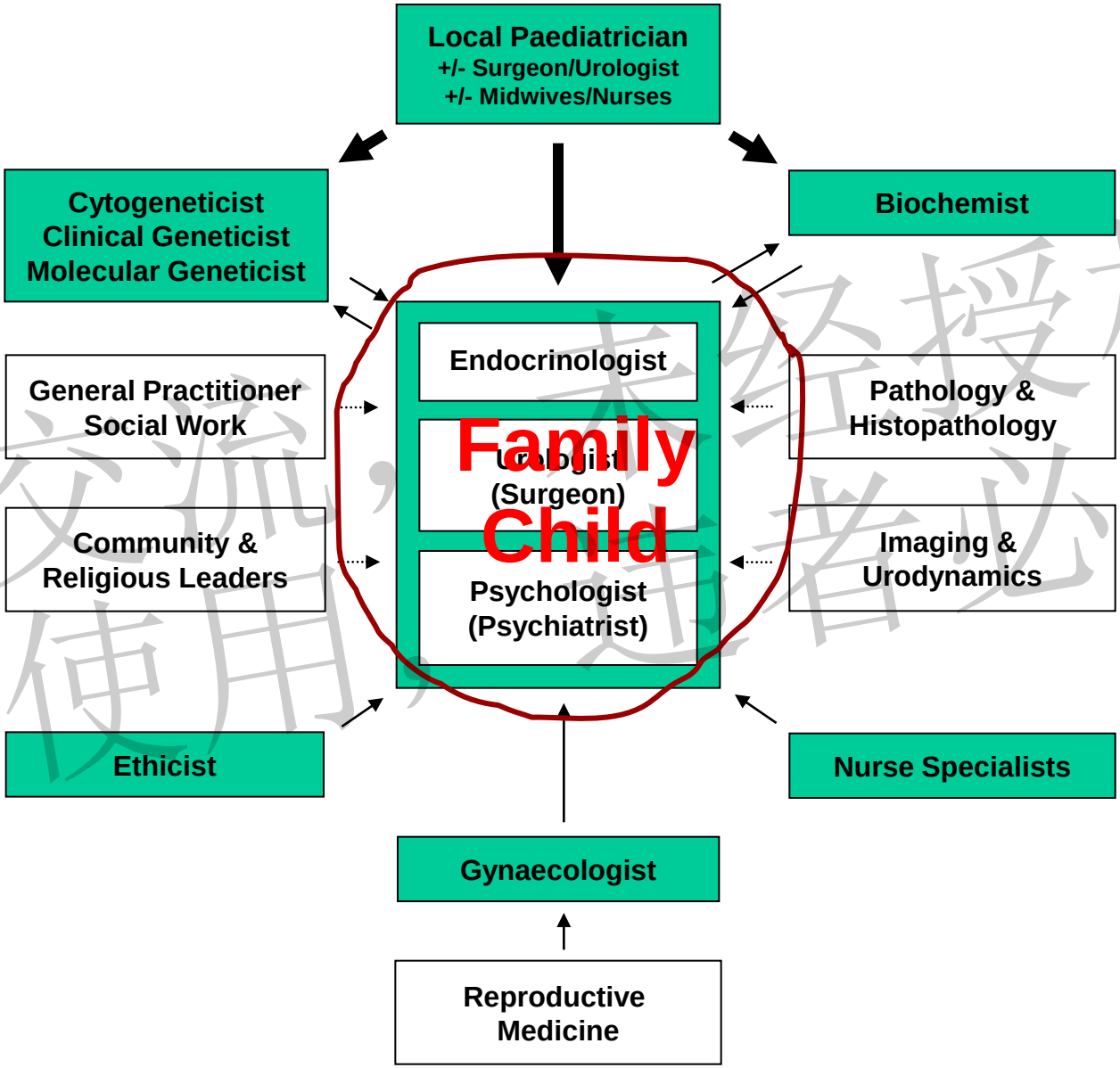
Interdisciplinary Team



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Management of DSD: medical

- Steroid replacement in CAH
- Testosterone in 46XY DSD
- Hormone replacement in puberty

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Management of DSD: surgical

- Clitoral reduction
- Vaginal reconstruction
- Hypospadias repair
- Gonadectomy

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Feminising Genital Surgery

- **Majority of babies with ambiguous genitalia assigned to a female sex of rearing will undergo feminising genital surgery in the first year of life.**
- **Management challenged recently from a clinical, ethical and social viewpoint**
- **Objective evidence to support this?**

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Rationale for Treatment of Ambiguous Genitalia "Optimal Gender Policy"

- **Surgery essential for "normal" psychosocial and psychosexual development**
- **Best performed before the age of 2 years as psychosexually "neutral"**
- **Gender recognition heavily dependent on unambiguous appearance of genitalia and unequivocal parental assurance**

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Aims of Surgery

- Normal appearance
- Good psychological & sexual outcomes
- Stable gender identity development
- Menstruation and sexual intercourse
- Prevention of urinary symptoms
- Relief of parental anxiety
- Prevention of bullying and teasing
- Avoid telling the child

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Are the aims of surgery achieved?

- Aims
  - Cosmetic
  - Anatomical
  - Sexual Function
  - Psychosocial and psychosexual
  - Quality of Life

- Scanty long term data

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Vaginoplasty for CAH

- **Most results published on CAH with no objective assessment of sexual function**
- **High incidence of vaginal stenosis**
  - **Allen et al 1982 65% (n=23)**
  - **Gearhart et al 1992 79% (n = 28)**
  - **Alizai et al 1999 100% (n = 13)**
  - **Creighton 2001 98% (n=44)**

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Feminising childhood surgery for ambiguous genitalia

- **Creighton et al 2001 *Lancet***
  - **Objective cosmetic and anatomical outcome in 44 adolescents**
    - **98% would require further treatment**
    - **23% dilators**
    - **77% more surgery**
  - **Multiple operations**
    - **31% had 2 or more vaginoplasties**
    - **26% had 2 or more clitoral procedures**

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Available Objective Data on Outcomes of Clitoral Surgery

- **Dittman et al 1992**
  - **33% anorgasmia in CAH compared to non-CAH sisters**
- **May et al 1996**
  - **41% anorgasmia in CAH compared to 12% in diabetic women**
- **Minto et al 2003 Lancet**
  - **25% anorgasmia after surgery for ambiguous genitalia compared to 0% without surgery**

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Key Points

- Genital surgery is irreversible
- Infants cannot consent
- Clitoral surgery damages adult sexual function
- The majority of patients will require further major surgery at adolescence
- No data confirm that cosmetic genital surgery leads to a good psychosexual outcome

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Recommendations

- **Majority of vaginal surgery should be deferred until adolescence**
- **Information on potential damage to sexual function must be made available to parents considering surgery for their daughters**
- **Defer surgery for clitoromegaly especially if mild or moderate**

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CAIS tumor risk

- Ranges from 0.8% to 22%
- “Chicago Consensus”: 2%

Clinical Endocrinology (2012) 76, 894–898 doi: 10.1111/j.1365-2265.2012.0433

ORIGINAL ARTICLE

Timing of gonadectomy in adult women with complete androgen insensitivity syndrome (CAIS): patient preferences and clinical evidence

Rebecca Deans*, Sarah M. Creighton†, Lih-Mei Liao† and Gerard S. Conway†

- Literature review > 20y: 14%
- “Very limited evidence to advise”

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Genetics

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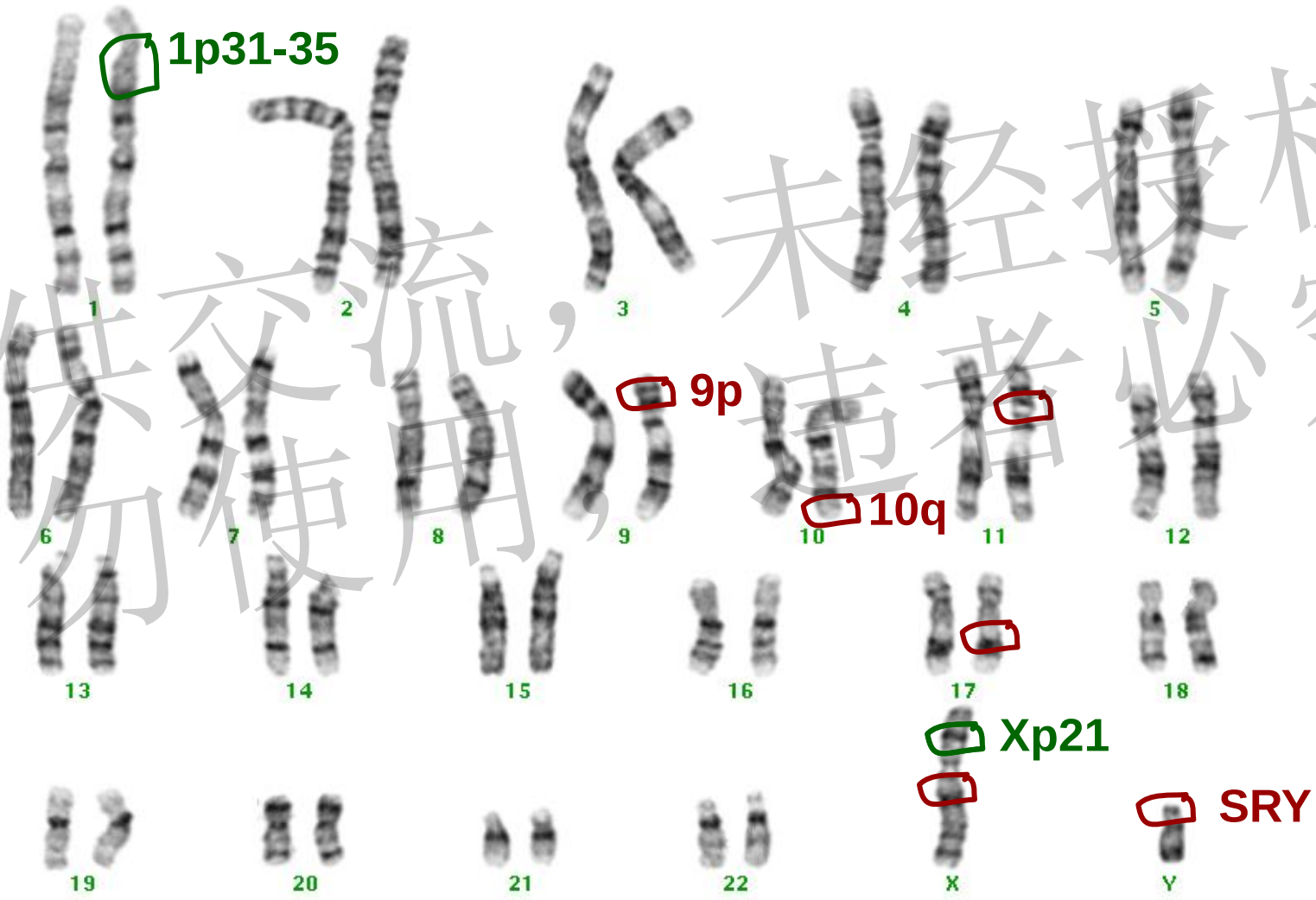
Common Changes (46,XY DSD)



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Strategies for gene identification

Candidate gene approach

- Mouse models
  - Naturally-occurring
  - Transgenic
- Chromosomal abnormalities
- Genome Mapping Strategies
  - Linkage analysis
  - Comparative Genomic Hybridization
  - SNP arrays

Next generation sequencing

- Targeted sequencing
- Whole exome sequencing
  - *FOG2/ZFPM2*
  - *HHAT*
- Whole genome sequencing

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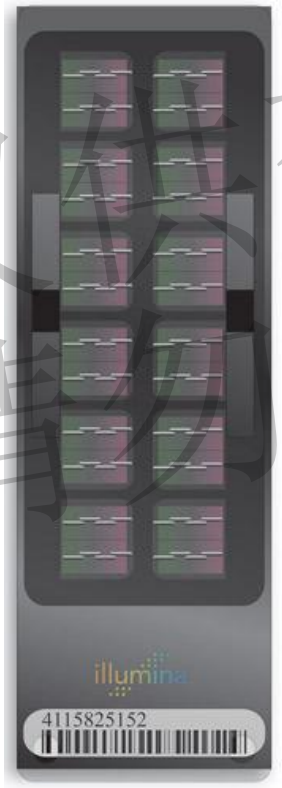
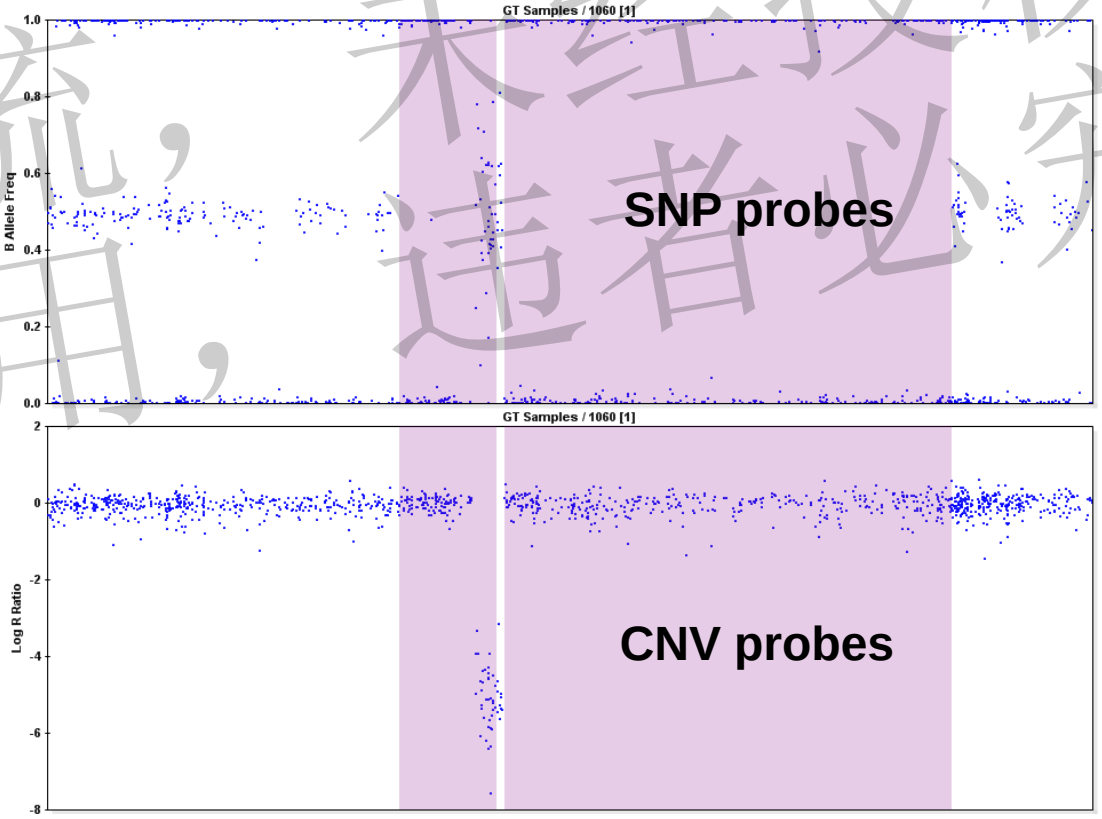
SNP/CNV arrays

Does not pick up balanced translocations, inversions and low level mosaicism

Illumina 610Quad



Deletion



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NGS: Strategy for evaluating genetic changes

DNA → RNA → Protein

- **Is the variant heterozygous or homozygous?**
- **Which chromosome does it lie on?**
- **Does the variant lead to an amino acid change?**
- **Is the residue highly conserved between species?**
- **Can it affect splicing?**
- **Is it likely to be deleterious to protein function?**
- **Is it present in controls eg ExAC, EVS, dbSNP, 1000 genomes?**
- **Is it expressed in the right tissues?**
- **Is there an animal model with functional impairment?**
- ***In vitro* functional studies need to show functional impairment**

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Challenges of NGS

- Costly
- High number of variants
  - 15,000-20,000 in coding region in WES
  - 3-4 million variants in whole genome sequencing
- Bystander effects
  - Variants in genes that are not relevant to DSD but which could have health-related consequences
- Careful filter selection
- Exclude variants with a frequency of 1% or more in control/reference populations as well as synonymous or non-coding variants
- Potentially deleterious variants identified in 3.4% of normal European populations and 1.2% in those of African descent

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Transition

ADULT DSD

- Gynaecologist
- Urologist
- Psychologist
- Endocrinologist
- Imaging
- Histopathologist

- Transition/FU DSD
- New presenters

- Long term management of complex anatomy

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Challenges of DSD –the way forward

- **Long-term outcomes – medical, psychosocial, surgical**
- **Collaborations - clinical, genetics**
- **Antenatal diagnosis – circulating cell free fetal DNA to sex the fetus and to diagnose monogenic disorders eg CAH**
- **Identification of new genes – only 20% cases genetically characterised**
- **Identification of genetic modifiers, epigenetic phenomena, gene-environment interactions**

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Acknowledgements

John Achermann

Sarah Creighton

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