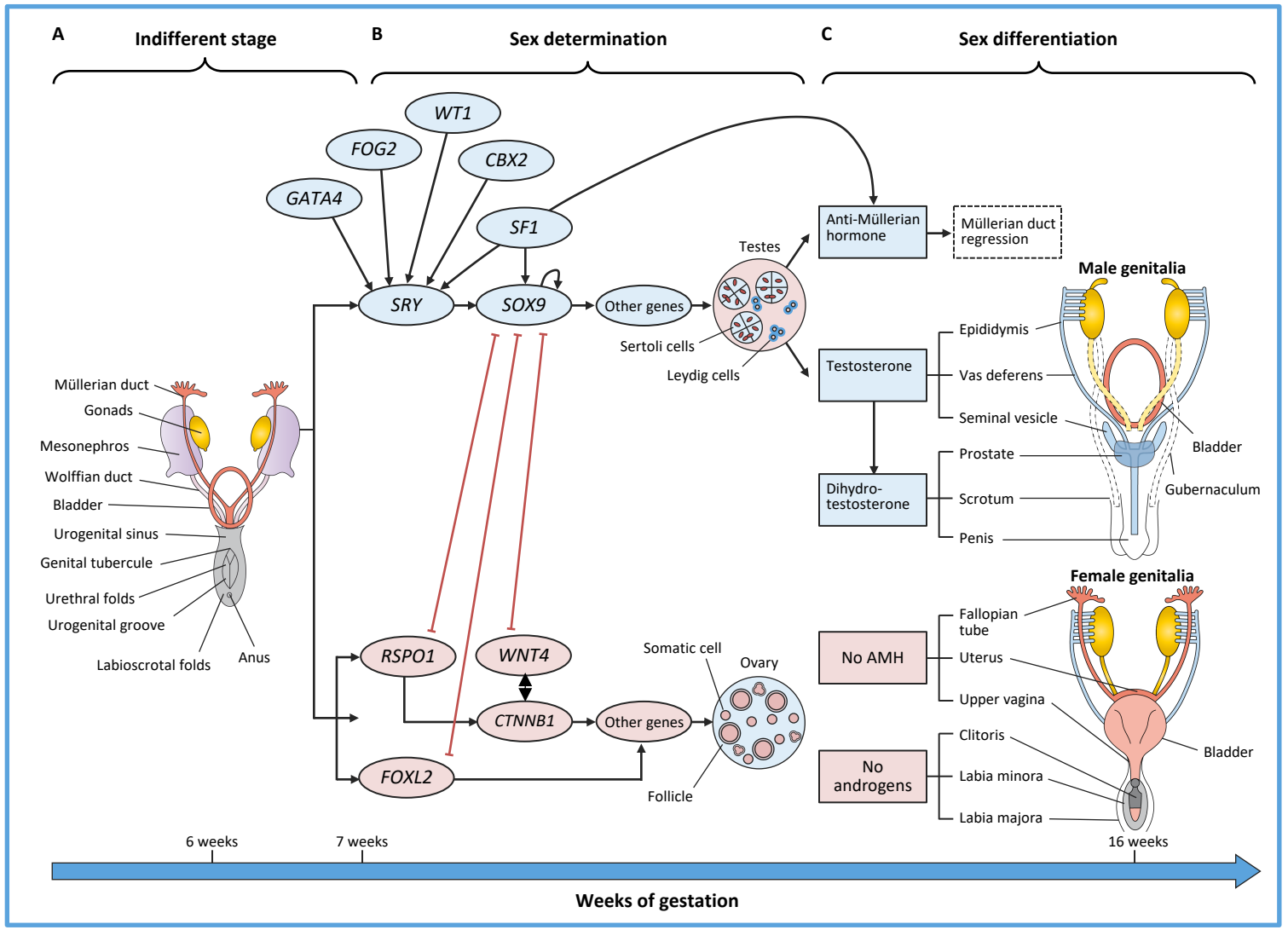
DIFFERENCES OF SEX DEVELOPMENT

Carla Bizzarri, MD
Unit of Endocrinology
Bambino Gesù Children's Hospital, Rome, Italy

I have no conflicts of interest to disclose

EMBRYOGENESIS OF HUMAN GENITALIA



- At 5-6 weeks gestation **(A)** indifferent stage:
  - Bipotential gonads are formed
  - Externally:
    - genital tubercle
    - urethral folds flank the urogenital groove
    - labioscrotal folds
  - Internally Müllerian and Wolffian ducts are present
- Sex determination occurs at 7 weeks **(B)**
  - Differential gene activation and downstream signalling
  - Somatic cells and gonocytes differentiate into testicular or ovarian cell types
- During sex differentiation **(C)**:
  - Hormone-dependent differentiation of external and internal genitalia
- Testes present:
  - Wolffian ducts give rise to the male reproductive tract and Müllerian ducts regress
- No testes (irrespective of the existence of ovaries):
  - Wolffian ducts degenerate while Müllerian ducts give rise to the female internal genitalia

Arrows indicate gene activation and truncated lines signify gene repression
AMH, anti-Müllerian hormone; CBX2, chromobox homologue 2; CTNNB1, Catenin β-1; FOG2, friend of GATA protein 2; FOXL2, Forkhead box L2; GATA4, GATA-binding protein 4; RSPO1, R-spondin 1; SF1, steroidogenic factor 1; SOX9, SRY-box 9; SRY, sex-determining region Y; WT1, Wilms' tumour 1; WNT4, Wnt family member 4
León NY, et al. Lancet Diabetes Endocrinol. 2019;7(7):560-74

DSD: CLASSIFICATION

The classification divides DSDs in 3 categories:

- 46,XX DSD that includes virilised females and XX sex reversal
- 46,XY DSD that includes patients with abnormal testicular differentiation and XY sex reversal
- Sex chromosome DSD that includes:
  - Turner Syndrome
  - Klinefelter Syndrome
  - 45,X/46,XY gonadal dysgenesis
  - Ovotesticular disorders

DSD, differences of sex development

Feldman Witchel S, et al. Best Pract Res Clin Obstet Gynaecol. 2018;48:90-102; Hughes IA, et al. Arch Dis Child. 2006;91(7):554-63

HORMONAL AND NON-HORMONAL DSD

HORMONAL DSDs

- Gonadal dysgenesis–Denys-Drash syndrome; Frasier syndrome; WAGR syndrome; ATRX syndrome; Turner syndrome; Swyer syndrome; Perrault syndrome; and campomelic dysplasia with autosomal sex reversal
- Hypogonadism–Klinefelter syndrome; Noonan syndrome; Kallmann syndrome; CHARGE syndrome; Prader-Willi syndrome; congenital adrenal hypoplasia; and Fraser syndrome
- Abnormal cholesterol metabolism;–Smith-Lemli-Opitz syndrome and desmosterolosis

NON-HORMONAL DSDs

Internal genitalia affected

- Wolffian duct anomalies–variants in CFTR
- Müllerian duct anomalies–Mayer-Rokitansky-Küster-Hauser syndrome types 1 and 2, Herlyn-Werner-Wunderlich syndrome, genital-renal-ear-skeletal syndrome and hand-foot-uterus syndrome

External genitalia affected

- Defects of the lower abdominal wall–bladder exstrophy and epispadias complex
- Perineum defects

Coacal anomalies–OEIS complex

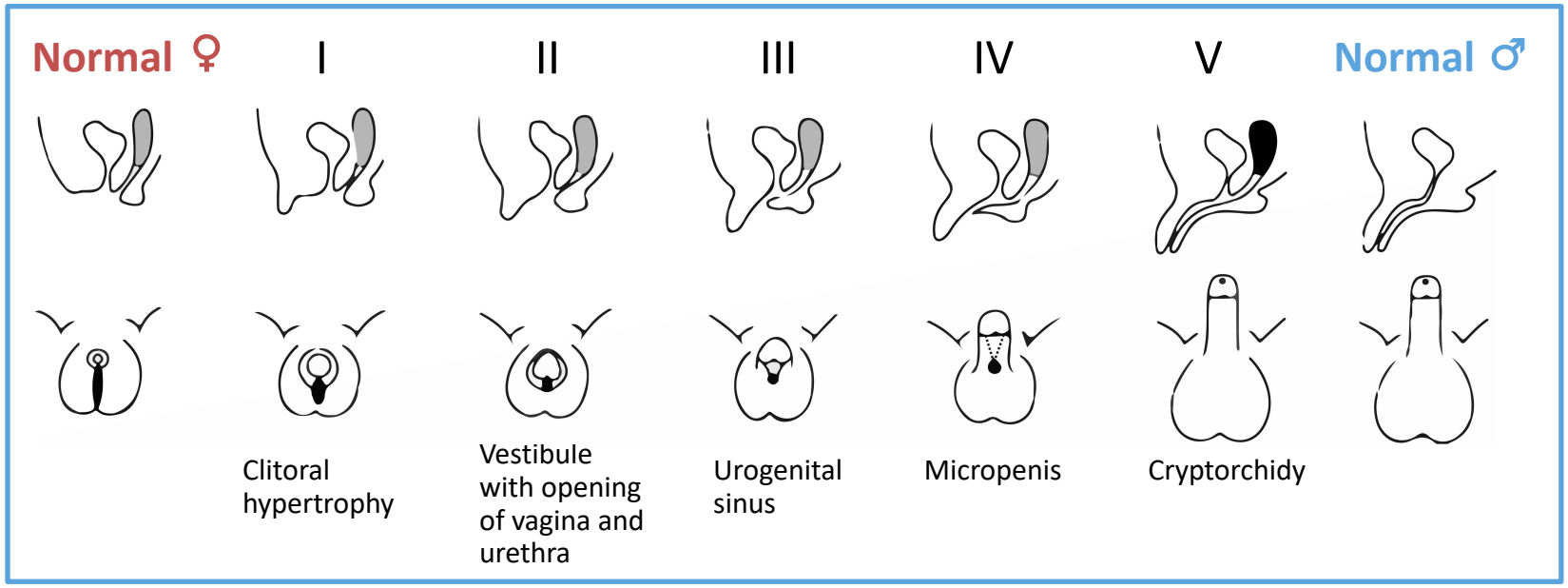
Caudal regression syndrome

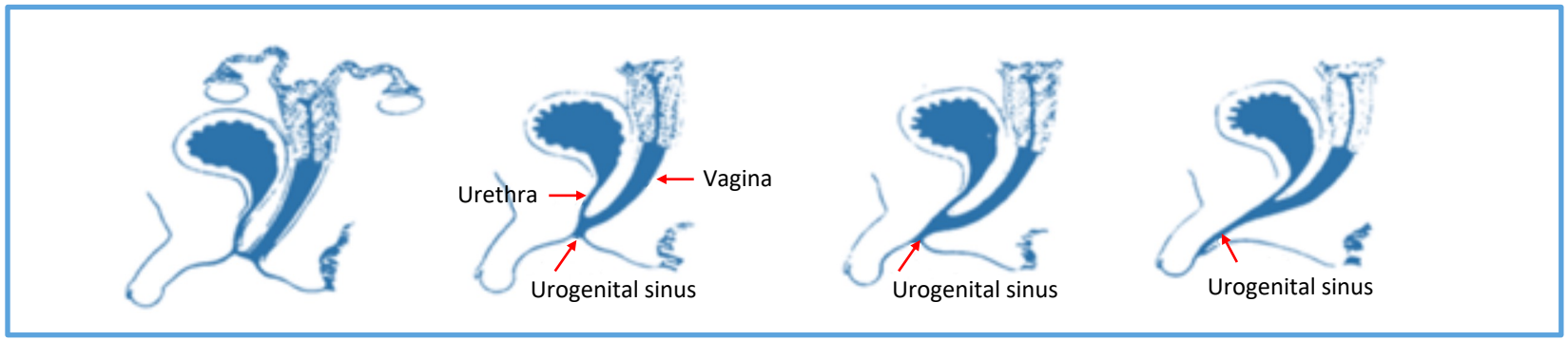
Sirenomelia

ATRX, α-thalassemia mental retardation; CHARGE, coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities; CFTR, cystic fibrosis transmembrane conductance regulator; DSD, differences of sex development; OEIS, omphalocele, exstrophy of the cloaca, imperforate anus, and spinal defects; WAGR, Wilms' tumour, aniridia, genitourinary abnormalities, and mental retardation

León NY, et al. Lancet Diabetes Endocrinol. 2019;7(7):560-74

DIFFERENT DEGREES OF VIRILIZATION ACCORDING TO THE PRADER'S STAGES





- **Prader stage 0:** normal external genitalia
- **Prader stage I:** slightly enlarged clitoris
- **Prader stage II:** mild degree of virilization
- **Prader stage III-V:** ambiguous genitalia
- **Prader VI stage:** normal male presentation with typical external genitalia and normal testes in the scrotum

Prader A. Helv Paediatr Acta 1954;9:231–48

THE EXTERNAL MASCULINISATION SCORE

Scoring of individual features of external genitalia by EMS

	Micro-penis	Scrotal fusion	Urethral meatus	Left gonad	Right gonad
3	No	Yes	Normal		
2.5					
2			Distal		
1.5				Labioscrotal	Labioscrotal
1			Mid	Inguinal	Inguinal
0.5					
0	Yes	No	Proximal	Abdominal or absent on examination	Abdominal or absent on examination

- EMS provides rates the extent of masculinisation of external genitalia
- Individual features are scored
  - phallus size
  - labioscrotal fusions
  - site of the gonads and location of urethral meatus
- Final score out of 12

EMS, external masculinization score

Ahmed SF, et al. BJU Int. 2000;85(1):120-4

EXTERNAL GENITALIA SCORE

Scoring of phenotypic features according to EGS

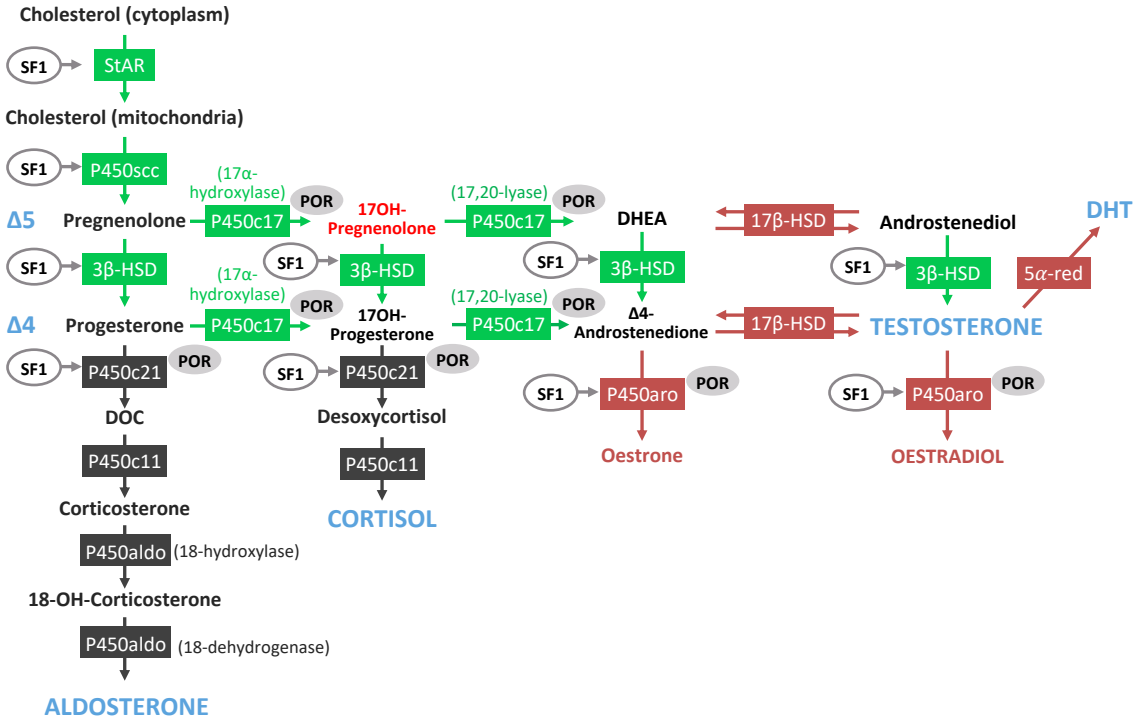
	Labioscrotal fusion	Genital tubercle length (mm)	Urethral meatus	Left gonad	Right gonad
3	Fused	>31	Top of the GT		
2.5		26-30	Coronal/glandular		
2		21-25	Along the GT		
1.5	Posterior fusion		At the GT base	Labioscrotal	Labioscrotal
1		10-20	Labioscrotal	Inguino-labioscrotal	Inguino-labioscrotal
0.5				Inguinal	Inguinal
0	Unfused	<10	Perineal	Impalpable	Impalpable

- Applied typical babies of both sexes and in babies who have variations in their genitalia
- Phenotypic features at 5 anatomical landmarks of the genitalia:
  - degree of labioscrotal fusion
  - length of the genital tubercle
  - position of the urethral meatus
  - location of the right and left gonad
- Final score = sum of points of 5 features

EGS, external genitalia score; GT, genital tubercle

van der Straaten S, et al. J Clin Endocrinol Metab. 2020;105(3):dgz142

DEFECTS OF GONADAL AND ADRENAL STEROIDOGENESIS INVOLVED IN DSD



GREEN: steps that are common to adrenals and gonads

RED: steps related to gonadal steroids

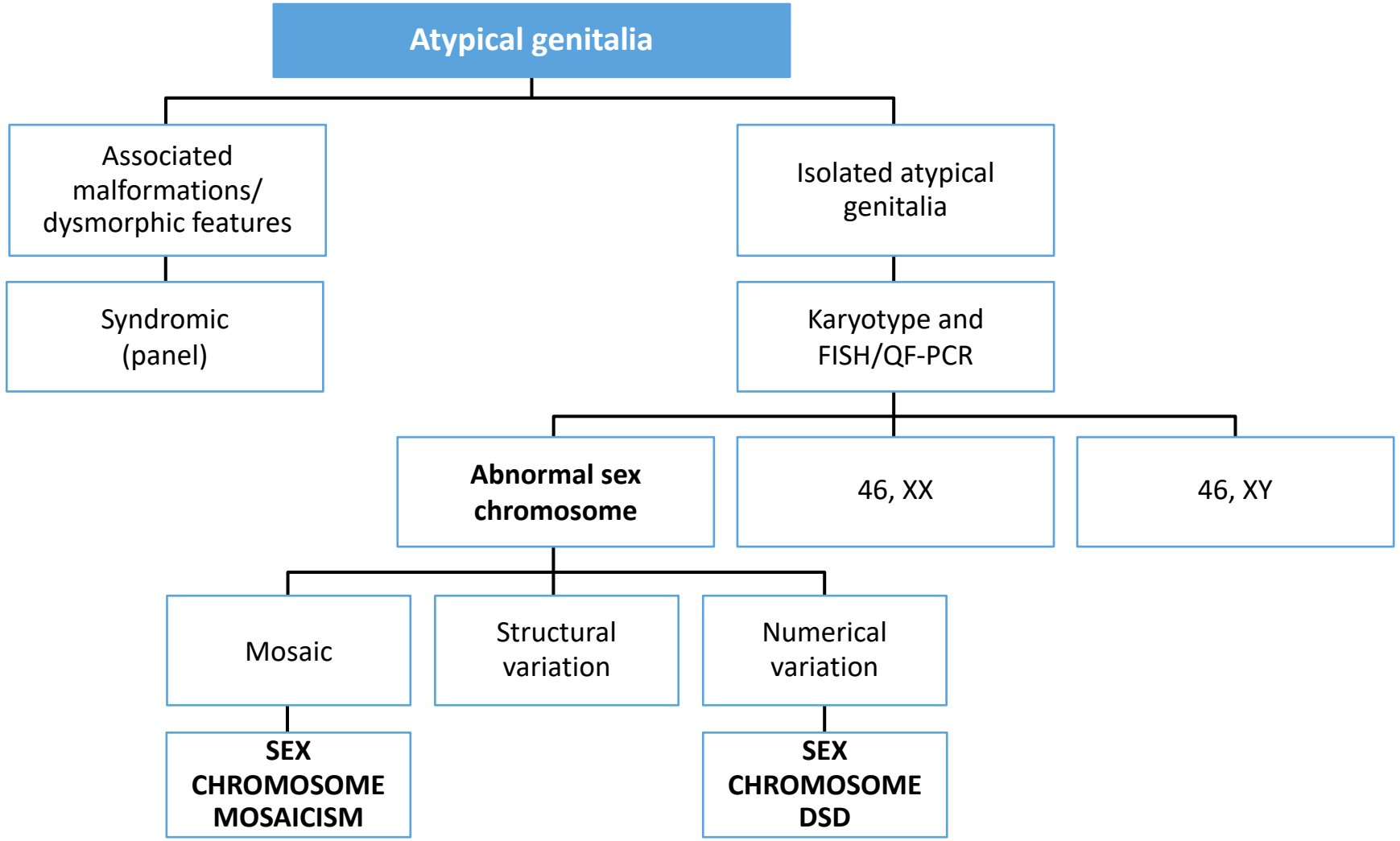
DARK GREY: steps related to adrenal steroids

Gene	Locus	Enzyme	Mutation phenotype	Ambiguous genitalia	
				XX	XY
CYP11A1	15q24.1	Cholesterol side-chain cleavage enzyme, mitochondrial	Congenital adrenal insufficiency	✗	✓
CYP11B1	8q24.3	Cytochrome P450 11B1, mitochondrial	Congenital adrenal hyperplasia	✓	✗
CYP17A1	10q24.32	Steroid 17-α-hydroxylase	Congenital adrenal hyperplasia	✗	✓
CYP19A1	15q21.2	Aromatase	XX DSD androgen excess aromatase deficiency	✓	✗
CYP21A2	6p21.33	Steroid 21-hydroxylase	Congenital adrenal hyperplasia	✓	✗
CYPB5A	18q22.3	Cytochrome B5	Methemoglobinemia and ambiguous genitalia	✗	✓
DHCR7	11q13.4	7-dehydrocholesterol reductase	Smith-Lemli-Opitz syndrome	✗	✓
DHCR24	1p32.3	Δ24-Sterol reductase	Desmosterolosis	✓	✓
HSD3B2	1p12	3β-hydroxysteroid dehydrogenase type 2	Congenital adrenal hyperplasia	✓	✓
HSD17B3	9q22.32	Testosterone 17-β-dehydrogenase 3	17β-HSD3 deficiency	✗	✓
POR	7q11.23	Cytochrome P450 reductase	Antley-Bixler syndrome with genital anomalies and disordered steroidogenesis	✓	✓
SRD5A2	2p23.1	3-Oxo-5-α-steroid 4-dehydrogenase 2	Steroid 5α-reductase 2 deficiency	✗	✓
STAR	8p11.23	Steroidogenic acute regulatory protein	Lipoid adrenal hyperplasia	✗	✓

3β-HSD, 3β-hydroxysteroid dehydrogenase; 5α-red, 5α-reductase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; DOC, desoxycorticosterone; DSD, differences of sex development; P450aldo, cytochrome P450 aldosterone synthase; P450aro, cytochrome P450 aromatase; P450c11, cytochrome P450 11β-hydroxylase; P450c17, cytochrome P450 17α-hydroxylase/17,20-lyase; P450c21, cytochrome P450 21-hydroxylase; P450scc, cytochrome P450 steroid sidechain cleavage; POR, cytochrome P450 oxidoreductase; SF1, steroidogenic factor 1; StAR, steroidogenic acute regulatory protein

León NY, et al. Lancet Diabetes Endocrinol. 2019;7(7):560-74; Rey RA, et al. Best Pract Res Clin Endocrinol Metab. 2011;25(2):221-38

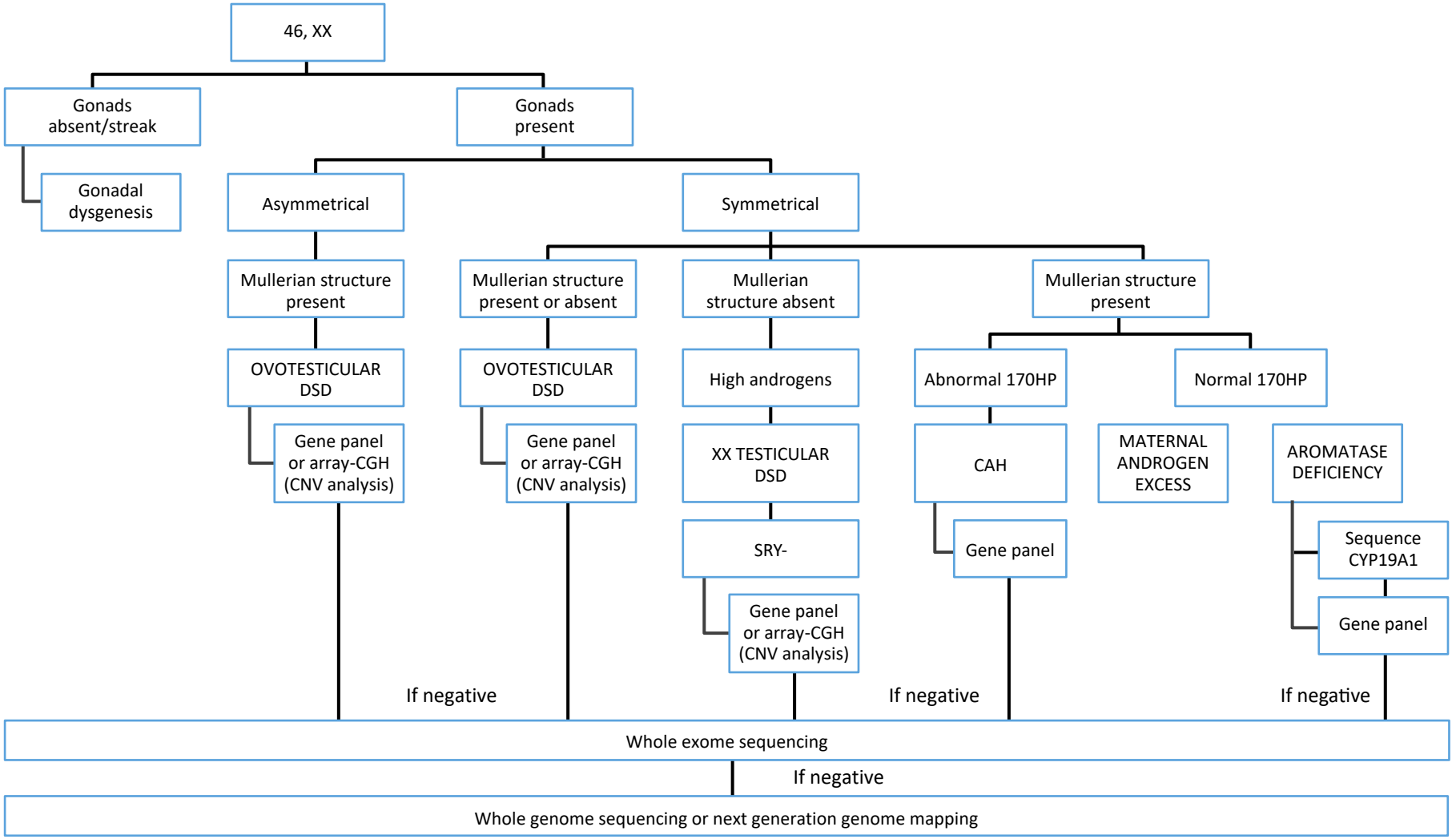
DIFFERENTIAL DIAGNOSIS OF DSD



DSD, differences of sex development; FISH/QF-PCR, fluorescence in situ hybridization/quantitative fluorescent polymerase chain reaction

Ibba A, et al. Minerva Pediatr (Torino). 2021. DOI: 10.23736/S2724-5276.21.06512-5

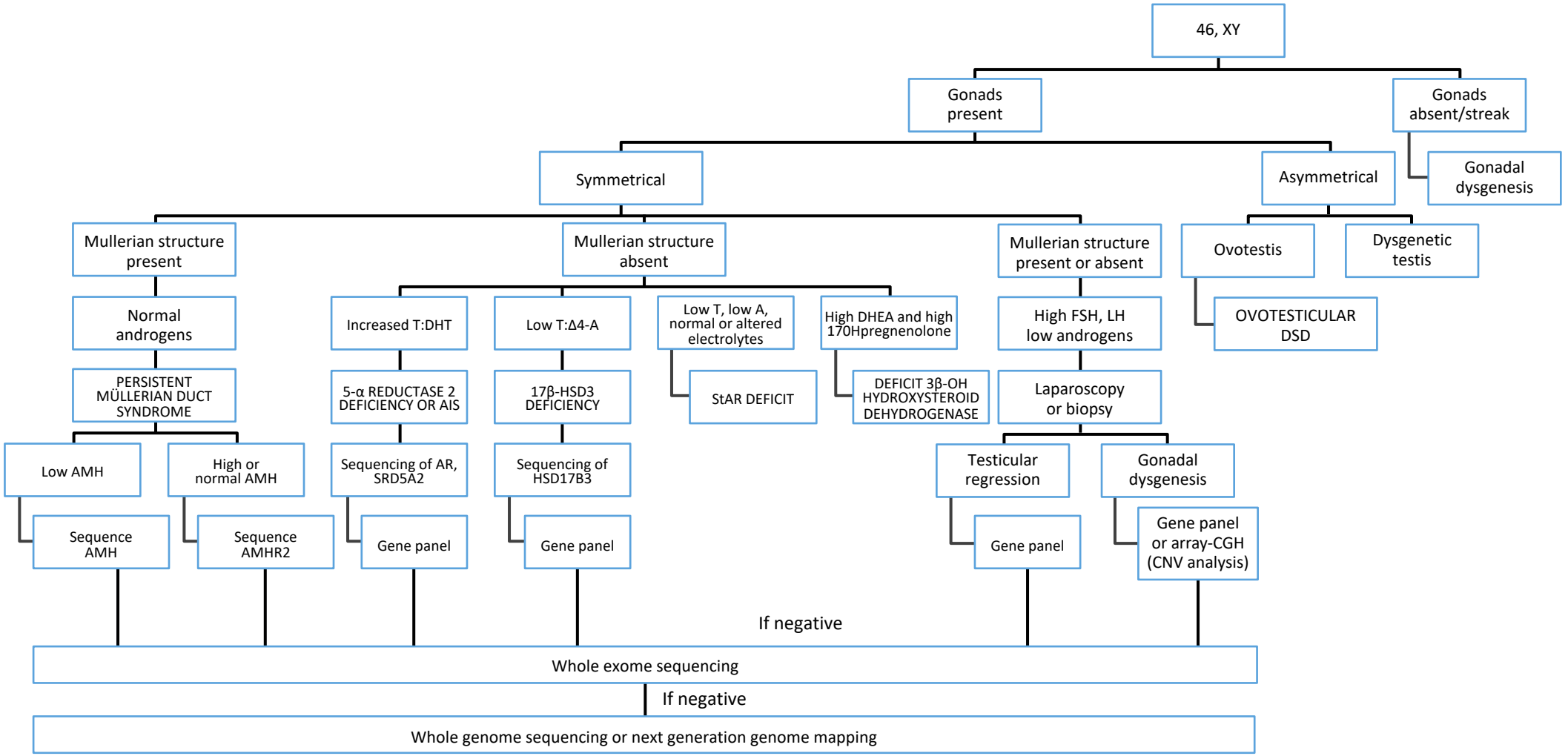
GENOMIC AND PHENOTYPIC EVALUATION OF 46XX DSD



CAH, congenital adrenal hyperplasia; CGH, comparative genomic hybridisation; CNV, copy number variation; DSD, differences of sex development; SRY-, sex-determining region Y negative

Ibba A, et al. Minerva Pediatr (Torino). 2021. DOI: 10.23736/S2724-5276.21.06512-5

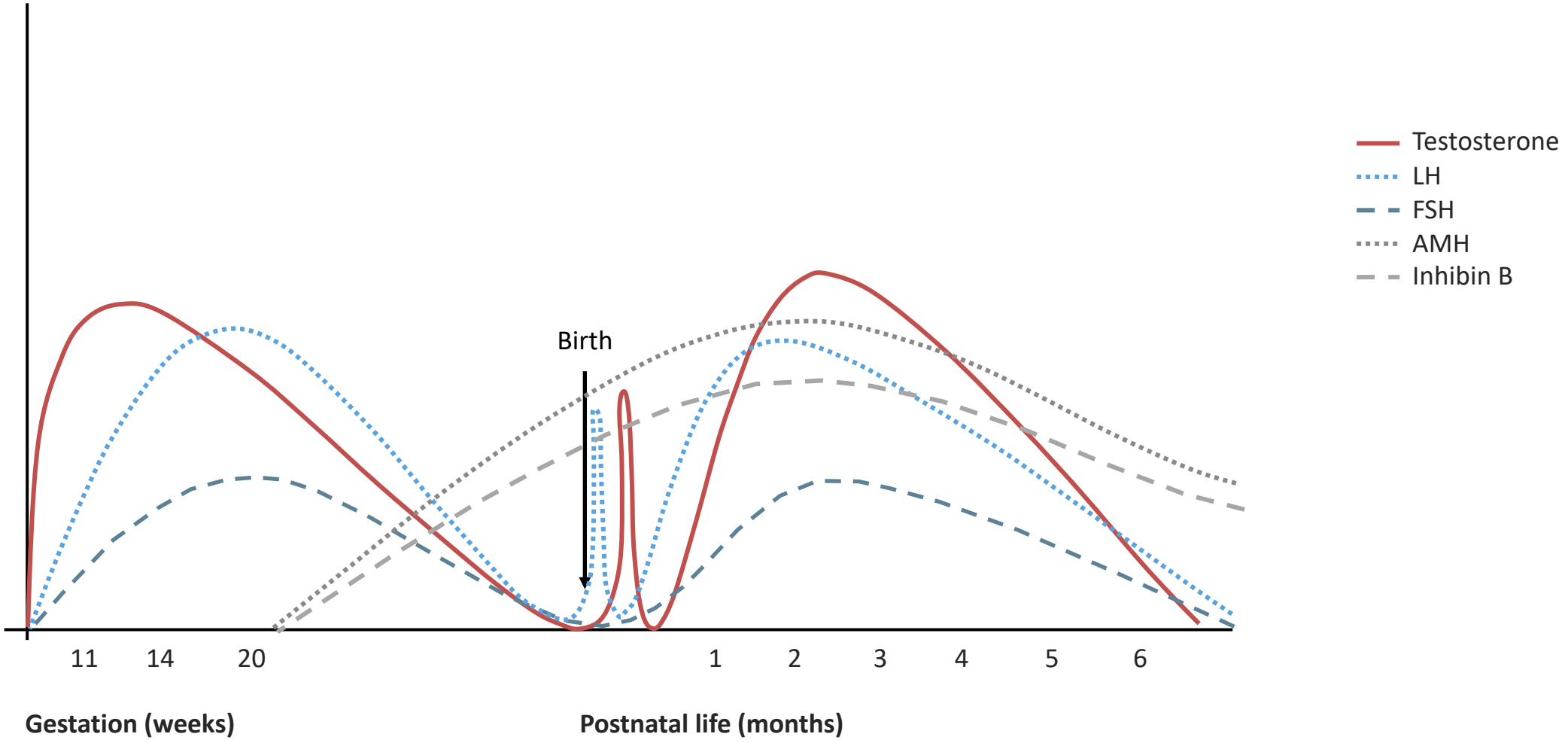
GENOMIC AND PHENOTYPIC EVALUATION OF 46XY DSD



, 5α-reductase type 2; StAR, steroidΔ4-A, Δ4-androstenedione; AIS, androgen insensitivity syndrome; AMH, anti-müllerian hormone; AMHR2, AMH receptor type 2; AR, androgen receptor; CGH, comparative genomic hybridisation; CNV, copy number variation; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; DSD, differences of sex development; FSH, follicle-stimulating hormone; LH, luteinizing hormone; Low-A, low androgen; SRD5A2ogenic acute regulatory protein; T, testosterone

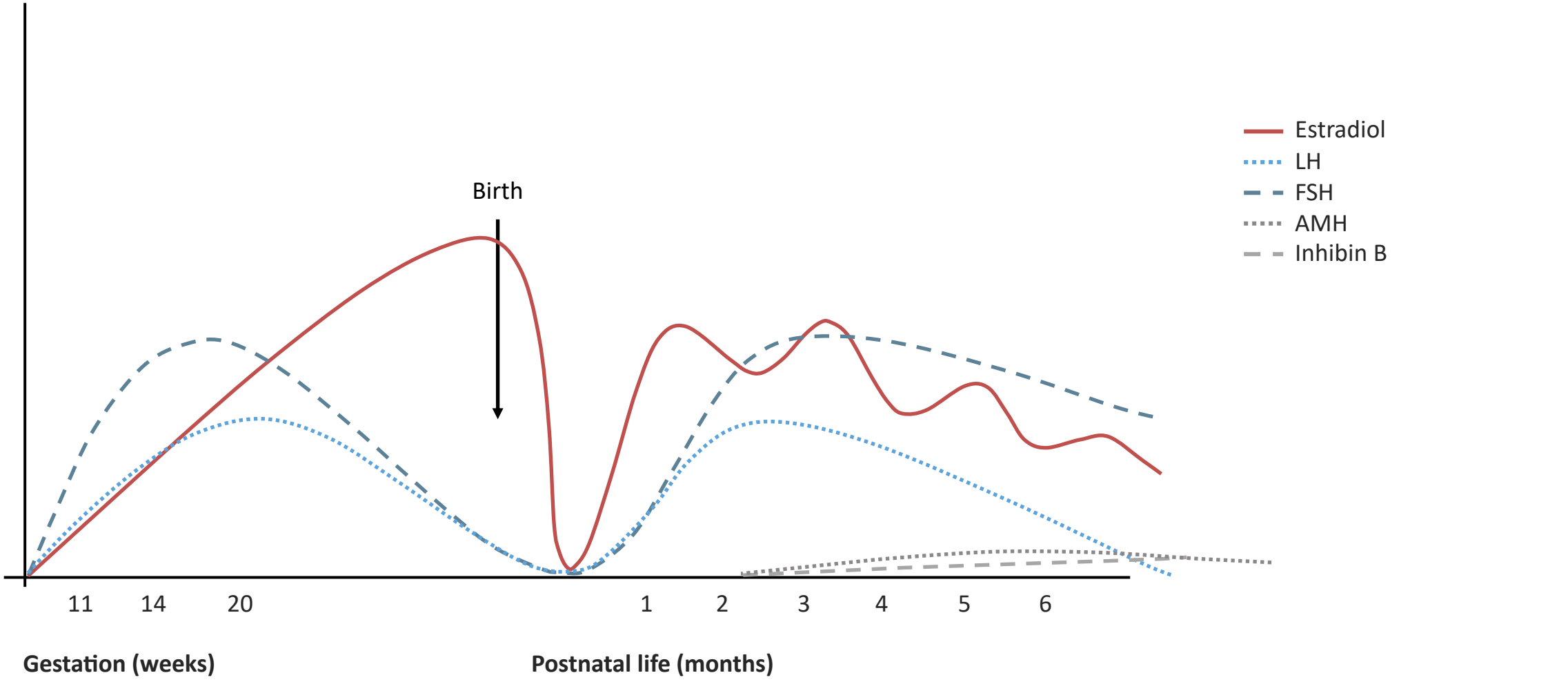
Ibba A, et al. Minerva Pediatr (Torino). 2021. DOI: 10.23736/S2724-5276.21.06512-5

HORMONAL CHANGES DURING MINIPUBERTY IN HEALTHY BOYS



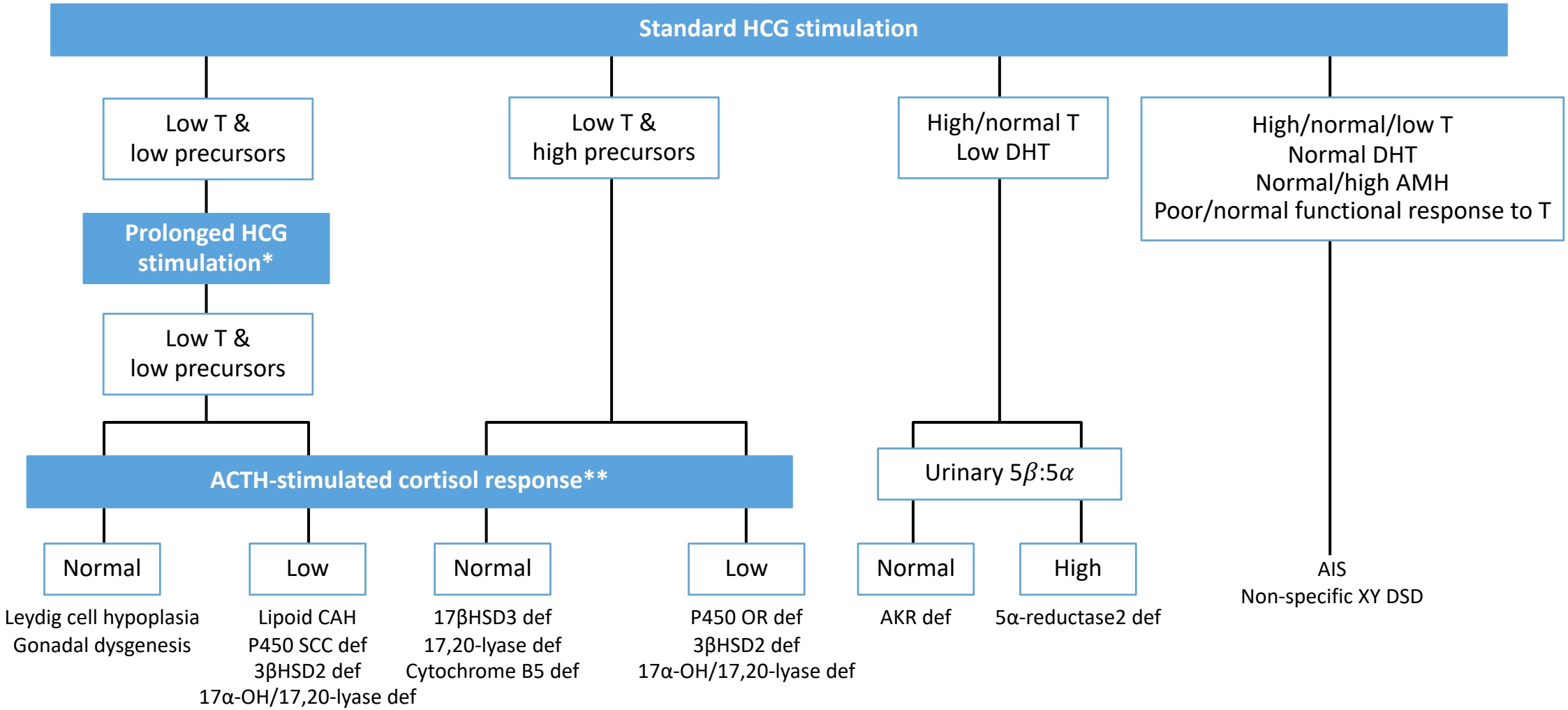
Bizzarri C, et al. Front Endocrinol (Lausanne). 2020;11:187

HORMONAL CHANGES DURING MINIPUBERTY IN HEALTHY GIRLS



Bizzarri C, et al. Front Endocrinol (Lausanne). 2020;11:187

INTERPRETATION OF HCG STIMULATION TESTS IN XY DSD

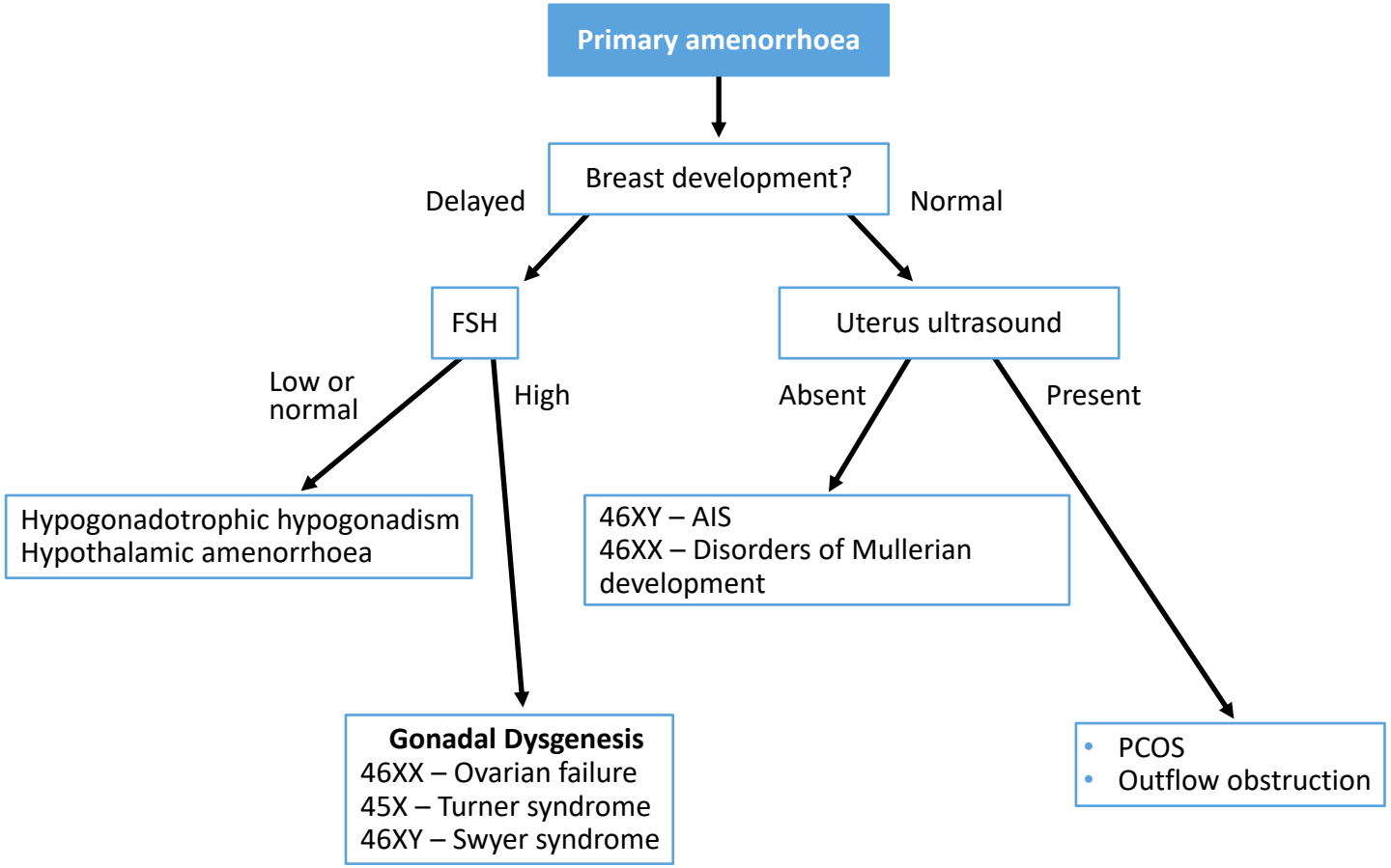


*A prolonged HCG stimulation test should be considered in those cases where there is a poor testosterone response to a standard HCG stimulation test or where a poor response is anticipated; **A synacthen stimulation test should be considered in those cases who show a poor testosterone response to hCG stimulation or if there is a clinical or biochemical suspicion of adrenal insufficiency

3βHSD2, 3β-hydroxysteroid dehydrogenase II; 17α-OH, 17α hydroxylase; 17βHSD3, 17β-hydroxysteroid dehydrogenase type 3; ACTH, adrenocorticotropic hormone; AIS, androgen insensitivity syndrome; AKR, aldoketoreductase; AMH, anti-müllerian hormone; CAH, congenital adrenal hyperplasia; def, deficiency; DHT, dihydrotestosterone; DSD, differences of sex development; HCG, human chorionic gonadotrophin; P450 OR, P450 oxidoreductase; SCC, sidechain cleavage; T, testosterone

Ahmed SF, et al. Clin Endocrinol (Oxf). 2021. DOI: 10.1111/cen.14528

APPROACH TO INVESTIGATING GIRLS WITH PRIMARY AMENORRHEA



AIS, androgen insensitivity syndrome; dvpt, development; FSH, follicle-stimulating hormone; PCOS, polycystic ovary syndrome

Ahmed SF, et al. Clin Endocrinol (Oxf). 2016;84(5):771-88

GENES WITH IDENTIFIED PATHOGENIC DSD MUTATIONS AND THEIR CLINICAL FEATURES

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GONAD DEVELOPMENT

Gene	Locus	Protein	Inheritance	Karyotype and phenotype	Genitalia and gonads	Others typical features
CBX2.2	17q25.3	Chromobox homologue 2 (isoform 2)	AR	XY gonadal dysgenesis	Complete gonadal dysgenesis	
EMX2	10q26.11	Empty spiracles homeobox 2	Monosomic deletion	XY gonadal dysgenesis		
*GATA4**	8p23.1	GATA-binding protein 4	AD	XY gonadal dysgenesis with or without congenital heart disease	Atypical genitalia, complete gonadal dysgenesis	Congenital heart defects (atrialseptum defects, ventricularseptum defects, tetralogy of Fallot), diaphragmatic hernia
NR5A1 (SF1)†*	9q33.3	Nuclear receptor subfamily 5, group A, member 1 (steroidogenic factor 1)	AD or AR	XX ovotesticular DSD (AD), XY gonadal dysgenesis partial or complete with or without adrenal failure (AD), premature ovarian failure type 7 (AD), spermatogenic failure type 8 (AD), and adrenal insufficiency (AR)	Complete gonadal dysgenesis, hypospadias, micropenis, cryptorchidism, primary ovarian insufficiency	
*WT1**	11p13	Wilms tumour1	AD	Denys-Drash syndrome, Frasier syndrome, nephrotic syndrome type 4, Wilms tumour type 1, XX ovotesticular DSD, and WAGR syndrome (contiguous gene deletion including WT1 and PAX6)	Streak gonads, atypical female genitalia, clitoromegaly, short and blind-ending vagina	Aniridia, intellectual disability, early-onset nephropathy
*ZFPM2 (FOG2)**	8q23.1	Zinc finger protein, FOG family member 2 (friend of GATA protein 2)	AD	XY gonadal dysgenesis	Atypical genitalia, complete gonadal dysgenesis	Congenital heart defects (atrial septum defects, ventricular septum defects, tetralogy of Fallot), diaphragmatic hernia

*Also involved in testis determination; †Also involved in ovary determination

AD, autosomal dominant; AR, autosomal recessive; DSD, differences of sex development; PAX6, paired box 6; WAGR, Wilms' tumour, aniridia, genitourinary abnormalities, and mental retardation

Ahmed SF, et al. Clin Endocrinol (Oxf). 2016;84(5):771-88; Baetens D, et al. Best Pract Res Clin Endocrinol Metab. 2019;33(3):101271; Bashamboo A, McElreavey K. Ann Endocrinol (Paris). 2010;71(3):177-82; Cannata G et al. Int J Mol Sci. 2021;22(12):6353; Clarkson PA, et al. J Med Genet. 1993;30(9):767-772; Diz OM et al. J Pers Med. 2021;11(6):562; Hirayama-Yamada K, et al. Am J Med Genet A 2005;135(1):47–52; Jay PY, et al. Dev Biol 2007;301(2):602–14; León NY, et al. Lancet Diabetes Endocrinol. 2019;7(7):560-74; Lin L, Achermann JC. 2008;2(4-5):200-209;Lipska-Ziętkiewicz BS. 2021 Available from: https://www.ncbi.nlm.nih.gov/books/NBK556455/; Sproll P, et al. Mol Genet Genomic Med. 2018;6(5):785-795; Yang YQ, et al., Med Sci Monit 2012;18(6):CR344–50.

GENES WITH IDENTIFIED PATHOGENIC DSD MUTATIONS AND THEIR CLINICAL FEATURES

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TESTIS DETERMINATION

Gene	Locus	Protein	Inheritance	Karyotype and phenotype	Genitalia and gonads	Others typical features
ARX	Xp21.3	Aristaless related homeobox	XL	XY - X-linked lissencephaly with atypical genitalia and Proud syndrome (agenesis of the corpus callosum with atypical genitalia and intellectual disability)		Lissencephaly, absent corpus callosum, early-onset intractable seizures, temperature instability
ATRX	Xq13.3	ATRX, chromatin remodeller	XL	α-thalassemia mental retardation syndrome	Complete gonadal dysgenesis, absent Müllerian structures	Dysmorphic features, intellectual disability, α-thalassaemia
CBX2.1	17q25.3	Chromobox homologue 2 (isoform 1)	AD	XY DSD		
DHH	12q13.12	Desert hedgehog	AR	XY gonadal dysgenesis and XY partial gonadal dysgenesis with or without minifascicular neuropahty	Complete or partial gonadal dysgenesis	Minifascicular neuropathy
DMRT1	9p24.3	Doublesex and mab-3 related transcription factor 1	Monosomic deletion	XY gonadal dysgenesis and XY ovotesticular DSD	Complete gonadal dysgenesis	Dysmorphic features, intellectual delay, microcephaly
MAP3K1	5q11.2	Mitogen-activated protein kinase kinase kinase 1	AD	XY gonadal dysgenesis		
NR0B1 (DAX1)	Xp21.2	Nuclear receptor subfamily 0, group B, member 1 (dosage-sensitive sex reversal)	XL	XY gonadal dysgenesis (NR0B1 duplications) and congenital adrenal hypoplasia	Complete gonadal dysgenesis with hypogonadotropic hypogonadism	Cleft palate, intellectual delay
SOX9	17q24.3	SRY-box 9	AD	Dysgenetic testis with campomelic dysplasia and XX ovotesticular DSD (SOX9 duplications)		Cooks syndrome, Pierre Robin sequence
SOX10	22q13.1	SRY-box 10	Not reported	XX ovotesticular DSD (SOX10 duplications)	Male external genitalia with hypospadias	Peripheral neuropathy; Waardenburg syndrome; Hirschsprung disease

AD, autosomal dominant; AR, autosomal recessive; DSD, differences of sex development; XL, X-linked

Ahmed SF, et al. Clin Endocrinol (Oxf). 2016;84(5):771-88; Baetens D, et al. Best Pract Res Clin Endocrinol Metab. 2019;33(3):101271; Bartels I, et al. Eur J Med Genet. 2013;56(8):458-62; Falah N et al. Am J Med Genet A. 2017;173(4):1066-1070; Gécz J, et al. Curr Opin Genet Dev. 2006;16(3):308-16; Gibbons, R. Orphanet J Rare Dis. 2006;1(15); Hartmann H, et al. Neuropediatrics. 2004;35:157-160; León NY, et al. Lancet Diabetes Endocrinol. 2019;7(7):560-74; Lin L, et al. J Clin Endocrinol Metab. 2006;91(8):3048-3054; Masuyama H, et al. Chromosome Res. 2012;20(1):163-76; O. Alfi GN, et al. Ann. Genet. 16 (1973) 17e22; Okazaki S, et al. Acta Neuropathologica. 2008;116(4),453–462; Rockich BE. PNAS 2013;110:E4456-E4464; Sato, NS, et al. Ann Clin Transl Neurol. 2017;4:415-421.

GENES WITH IDENTIFIED PATHOGENIC DSD MUTATIONS AND THEIR CLINICAL FEATURES

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MALE SEXUAL DIFFERENTIATION

Gene	Locus	Protein	Inheritance	Karyotype and phenotype	Genitalia and gonads	Others typical features
AMH	19p13.3	Anti-Müllerian hormone	AR	XY - Persistent Müllerian duct syndrome type 1		
AMHR2	12q13.13	Anti-Müllerian hormone receptor type 2	AR	XY - Persistent Müllerian duct syndrome type 2		
AR	Xq12	Androgen receptor	XL	XY - Androgen insensitivity syndrome complete (CAIS) or partial (PAIS)	CAIS: Female with blind vaginal pouch and testes PAIS: Atypical with blind vaginal pouch, isolated hypospadias, normal male with infertility (mild) and testes	
LHCGR	2p16.3	LH/HCG receptor	AR or AD	XY - Leydig cell hypoplasia with hypergonadotropic hypogonadism (AR) and precocious puberty (AD)	Female, hypospadias or micropenis	Under-androgenization with variable failure of sex hormone production at puberty

AD, autosomal dominant; AR, autosomal recessive; CAIS, complete androgen insensitivity syndrome; DSD, differences of sex development; HCG, human chorionic gonadotrophin; LH, luteinizing hormone; PAIS, partial androgen insensitivity syndrome; XL, X-linked

Ahmed SF, et al. Clin Endocrinol (Oxf). 2016;84(5):771-88; Hassan HA, et al. Hormones (Athens). 2020;19(4):573-579; Baetens D, et al. Best Pract Res Clin Endocrinol Metab. 2019;33(3):101271; Lanciotti L, et al. Int J Environ Res Public Health. 2019;16(7):1268; León NY, et al. Lancet Diabetes Endocrinol. 2019;7(7):560-74; Picard JY, Josso N. Reprod Fertil Dev. 2019;31(7):1240-1245.

GENES WITH IDENTIFIED PATHOGENIC DSD MUTATIONS AND THEIR CLINICAL FEATURES

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OVARY DETERMINATION

Gene	Locus	Protein	Inheritance	Karyotype and phenotype	Genitalia and gonads	Others typical features
BRCA2	13q13.1	BReast CAncer protein 2	?	XX	Complete ovarian dysgenesis, primary amenorrhea, hypergonadotropic hypogonadism	Microcephaly, cafè-au-lait spots, acute myelocyticleukemia
BMP15	Xp11.22	Bone morphogenetic protein 15	XL	Ovarian dysgenesis and premature ovarian failure type 4		
CTNNB1	3p22.1	Catenin β-1	Not reported	No gonadal phenotype reported		
FOXL2	3q22.3	Forkhead box L2	AD	Blepharophimosis, ptosis, epicanthus inversus syndrome Premature ovarian failure type 3		
NR2F2	15q26.2	Nuclear receptor subfamily 2 group F member 2	?	XX	Atypical genitalia, ovarian dysgenesis, ovotesticular DSD	Congenital heart disease
WNT4	1p36.12	Wnt family member 4	AD or AR	SERKAL syndrome (46, XX ovotesticular DSD with dysgenesis of kidney, adrenal glands, and lungs, AR), Müllerian aplasia and hyperandrogenism (AD), XX ovotesticular DSD (AD)		
RSPO1	1p34.3	R-spondin 1	AR	XX ovotesticular DSD with palmoplantar hyperkeratosis and squamous cell carcinoma of the skin		

AD, autosomal dominant; AR, autosomal recessive; DSD, differences of sex development; XL, X-linked

Ahmed SF, et al. Clin Endocrinol (Oxf). 2016;84(5):771-88; Baetens D, et al. Best Pract Res Clin Endocrinol Metab. 2019;33(3):101271; Carvalheira G, J Endocr Soc. 2019;3(11):2107-2113; León NY, et al. Lancet Diabetes Endocrinol. 2019;7(7):560-74; Weinberg-Shukron A et al. N Engl J Med. 2018;379(11):1042-1049.

GENES WITH IDENTIFIED PATHOGENIC DSD MUTATIONS AND THEIR CLINICAL FEATURES

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FEMALE SEXUAL DIFFERENTIATION

Gene	Locus	Protein	Inheritance	Karyotype and phenotype	Genitalia and gonads	Others typical features
FSHR	2p16.3	Follicle stimulating hormone receptor	AD or AR	XX - Ovarian hyperstimulation syndrome (AD) and ovarian dysgenesis (AR)	Hypergonadotropic ovarian dysgenesis	Primary ovarian insufficiency Male infertility
LHCGR	2p16.3	Luteinising hormone/ choriogonadotropin receptor	AR	XX - Luteinising hormone resistance with hypergonadotrophic hypogonadism		Under androgenization (female genitalia or hypospadias or micropenis) with variable failure of sex hormone production at puberty

AD, autosomal dominant; AR, autosomal recessive; DSD, differences of sex development

Ahmed SF, et al. Clin Endocrinol (Oxf). 2016;84(5):771-88; Arnhold IJ, et al. Clin Endocrinol (Oxf). 1999;51(6):701-7; Balkan M, et al. J Biomed Biotechnol. 2010;2010:640318; Baetens D, et al. Best Pract Res Clin Endocrinol Metab. 2019;33(3):101271; Kuechler A, et al. Eur J Hum Genet. 2010;18(6):656-661; León NY, et al. Lancet Diabetes Endocrinol. 2019;7(7):560-74.

GENES WITH IDENTIFIED PATHOGENIC DSD MUTATIONS AND THEIR CLINICAL FEATURES

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UNKNOWN FUNCTION IN SEX DEVELOPMENT

Gene	Locus	Protein	Inheritance	Karyotype and phenotype	Genitalia and gonads	Others typical features
BMP4	14q22.2	Bone morphogenic protein 4	AD	XY	Hypospadias	
ESR2	14q23.2-q23.3	Estrogen receptor 2	?	XY or XX	Female external genitalia, complete gonadal dysgenesis	Dysmorphic features, eye abnormalities, anal atresia, rectovestibular fistula ovarian dysgenesis, primary amenorrhea
FGFR2	10q26.13	Fibroblast growth factor receptor 2	AD	XY	Complete gonadal dysgenesis	Crouzon-like craniosynostosis
FRAS1	4q21.21	Fraser extracellular matrix complex subunit 1	AR	Fraser syndrome		
HARS2	5q31.3	Histidyl-tRNA synthetase 2, mitochondrial	AR	Perrault syndrome (ovarian or gonadal dysgenesis with sensorineural deafness)		
HHAT	1q32.2	Hedgehog acyltransferase	AR	XY	Complete gonadal dysgenesis	Dwarfism, chondrodysplasia, narrow, bell-shaped thorax, micromelia, brachydactyly, microcephaly with cerebellar vermis hypoplasia, facial anomalies, hypoplastic irides and coloboma of the optic discs
HOXA13	7p15.2	HomeoboxA13	AD	Hand-foot-uterus syndrome	Hypospadias in males, Müllerian duct fusion defects in females	Limb abnormalities
PSMC3IP	17q21.2	PSMC3 interacting protein	AR	Ovarian dysgenesis		Absence of spontaneous puberty, nephrotic syndrome
SOHLH1‡	9q34.3	Spermatogenesis and oogenesis specific basic helix-loop-helix 1	AR	Ovarian dysgenesis type 5		
SOX8	16p13.3	SRY-box 8	AD	XY	Complete gonadal dysgenesis	Male infertility, primary ovarian insufficiency
ZNRF3	22q12.1	Zinc and ring finger 3	?	XY	Partial and complete gonadal dysgenesis	

‡Related to folliculogenesis and spermatogenesis

AD, autosomal dominant; AR, autosomal recessive; DSD, differences of sex development

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CONCLUSIONS

- DSDs are genetically and clinically heterogeneous conditions that need thoughtful evaluation by a multidisciplinary team
- Molecular technologies can help to clarify the aetiology and facilitate the diagnosis of DSDs
- Early diagnosis allowing correct sex assignment is essential to:
  - adequately take care of these patients and their families
  - ensure the best possible quality of life
  - improve fertility chances
  - improve cancer prevention

DSD, differences of sex development