Mahidol University
Faculty of Medicine Ramathibodi Hospital

XX Male syndrome

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46,XX testicular DSD

- Known as XX male syndrome, or Chapelle syndrome
- First reported in 1964
- A condition in which person with two X chromosomes has a male appearance
- Prevalence: 1 in 20000 male births
- Approximately 2% of male infertility

Délot EC, Vilain EJ. Nonsyndromic 46,XX Testicular Disorders/Differences of Sex Development. 2003 Oct 30 [Updated 2022 May 26]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023.

Y Chromosome

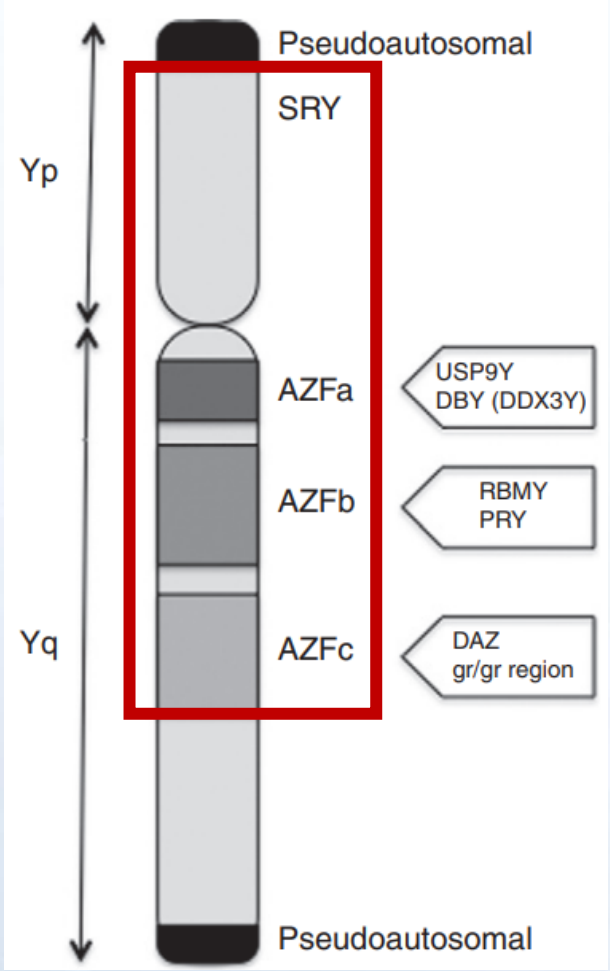
- Y chromosome contains many genes that are important in spermatogenesis and gonadal development

  SRY

  - Short arm of Y
  - The primary sex-determination gene

  AZF (Azoospermia factor)

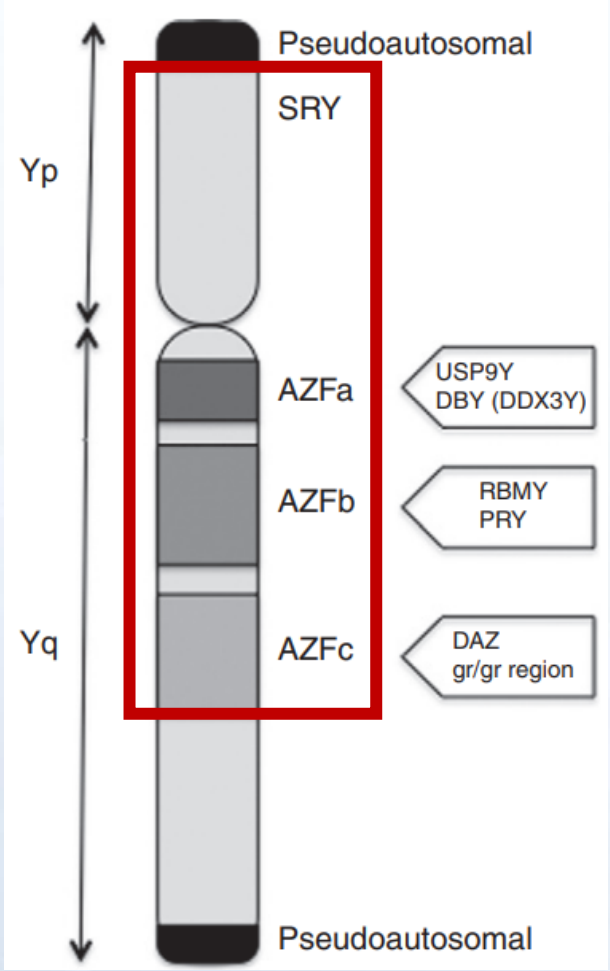
  - Long arm of Y
  - Essential for spermatogenesis



Colaco, S., Modi, D. Genetics of the human Y chromosome and its association with male infertility. *Reprod Biol Endocrinol* **16**, 14 (2018).

Pathogenesis

- Abnormal crossing between the distal portions of the short arms of the X and Y chromosomes during paternal meiosis
- These individuals transfers the TDF (testis determining factors) from Y chromosome to X chromosome
- They lack the azoospermia factor (AZF) region of the Y chromosome, which is essential for spermatogenesis



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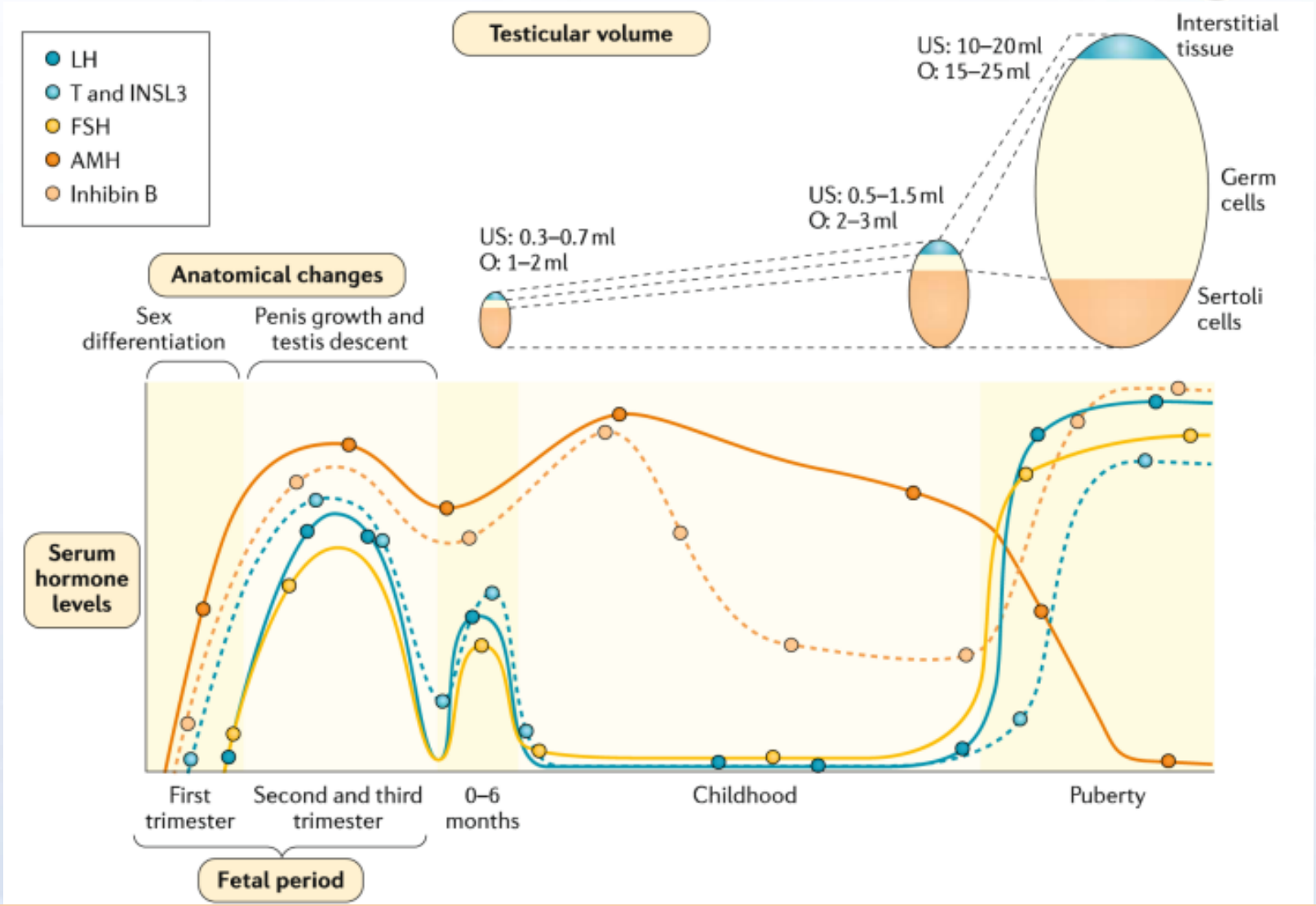
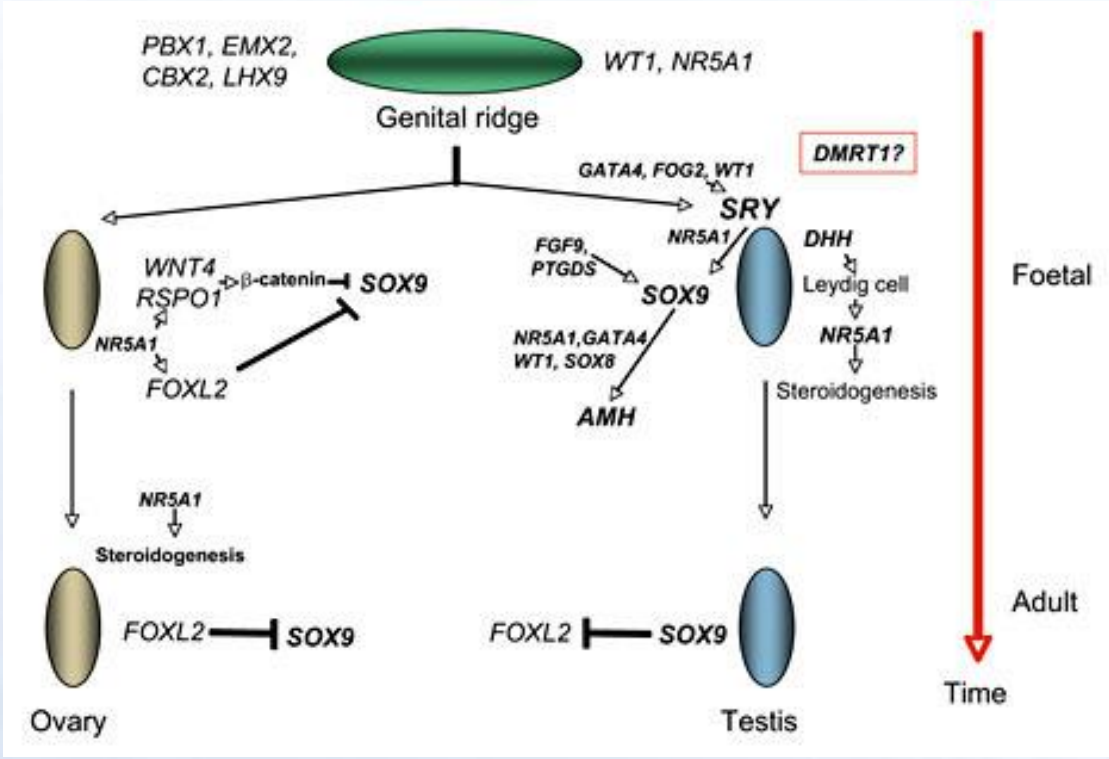


During puberty, testicular volume increases dramatically owing to spermatogenic development

Rey RA, Grinspon RP. Androgen Treatment in Adolescent Males With Hypogonadism. Am J Mens Health. 2020 May-Jun;14(3):1557988320922443.

Classification

- 80% *SRY*-positive
- 20% *SRY*-negative
  - Small copy number variants in *SOX3* or *SOX9*
  - Heterozygous pathogenic variants in *NR5A1* or *WT1*

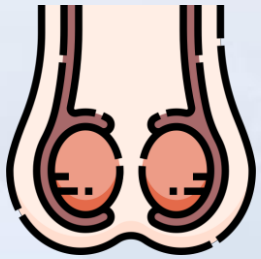


Gene regulation in gonadal development

Colaco, S., Modi, D. Genetics of the human Y chromosome and its association with male infertility. *Reprod Biol Endocrinol* **16**, 14 (2018).

Clinical features

- Mostly, Male external genitalia (normal penis size and pubic hair)
- 15% Ambiguous genitalia typically penoscrotal hypospadias
- Uncommon: anterior/distal hypospadias



- Typically descended testes but smaller and softer
- Uncommon: cryptorchidism

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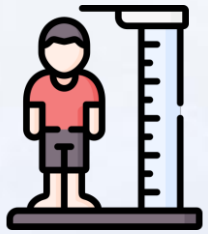
Clinical features

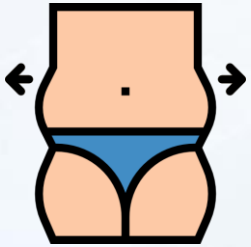
85% present after puberty, infertility is the most common presentation



Short stature

Low libido and erectile dysfunction

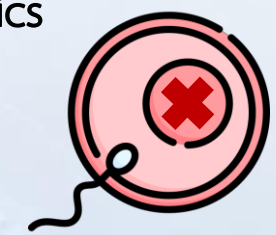
Decrease secondary male characteristics



Increase fat mass
Low muscle strength

Gynecomastia

Osteopenia



Infertility

Depression

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Increased risk of tumor

Extremely rare

- Leydig cell tumor
- Gonadoblastoma

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Investigation

For diagnosis	
LH, FSH, morning testosterone	Hypergonadotropic hypogonadism
Semen analysis	Azoospermia
Bone mineral density	High risk osteopenia
Karyotype analysis	46, XX
Gene-targeted testing	FISH or chromosomal microarray analysis for *SRY* gene
Pelvic ultrasound or MRI	No Müllerian structure

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Treatment

Hypogonadism	Initiate low dose testosterone after 14 years old Testosterone enanthate 100 mg IM q 3-4 wk then titration
Gynecomastia	Reduction mammoplasty if psychological distress
Osteopenia/osteoporosis	As osteoporosis guideline
Undervirilization	Consult urologist for orchidopexy and/or hypospadias repair
Infertility	Artificial insemination or *in vitro* fertilization using donor sperm Adoption
Psychological distress	Consult psychiatrist

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