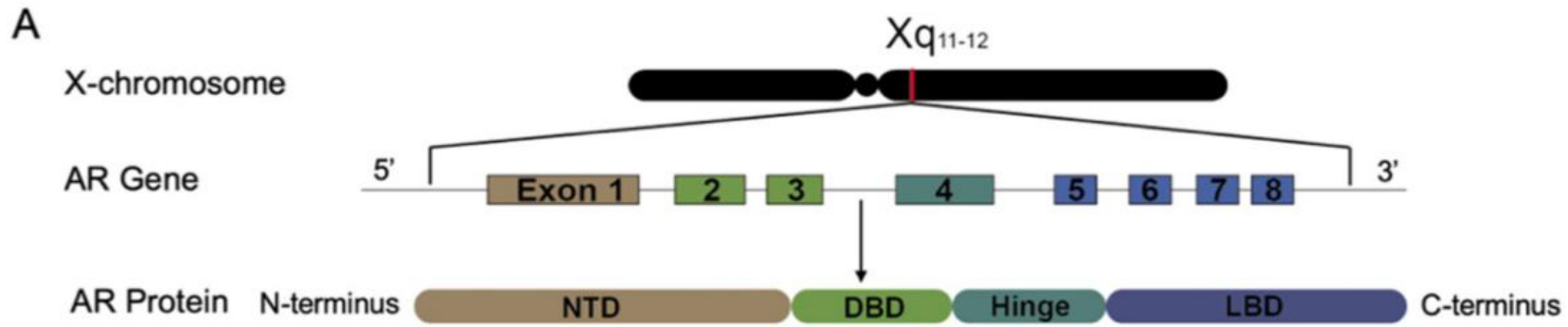
Interhospital Conference

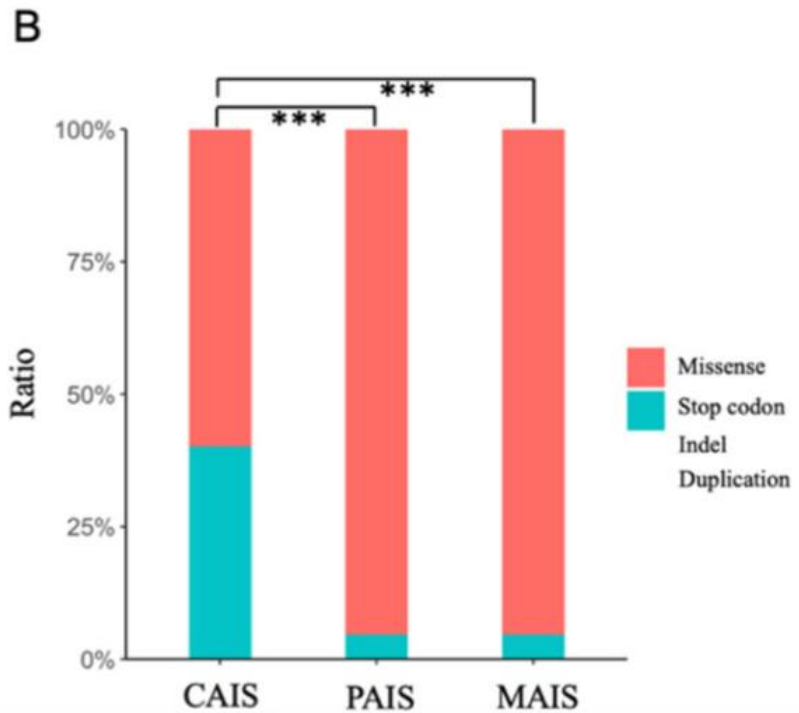
01/08/2025

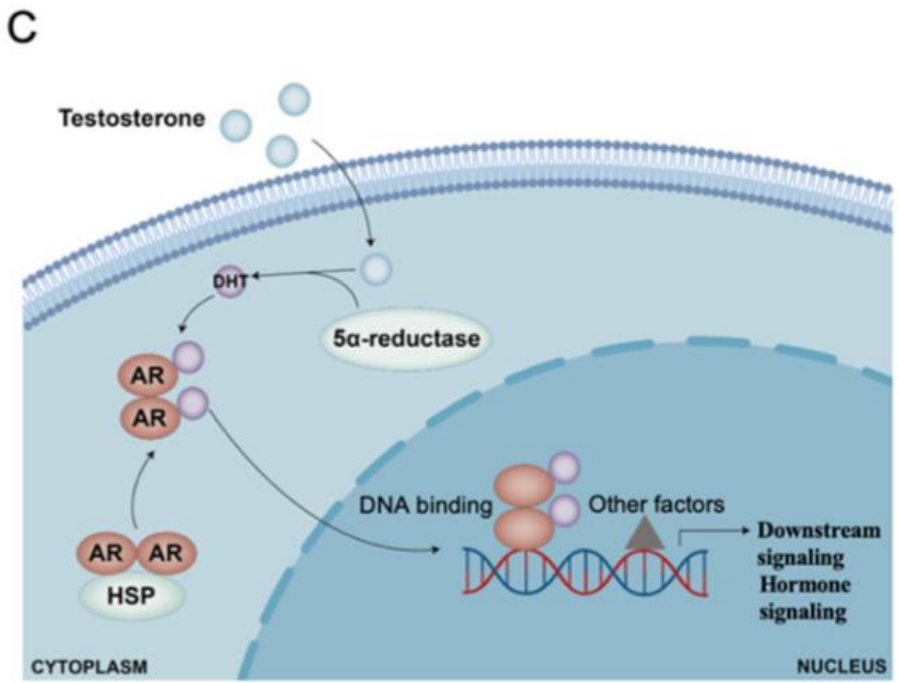
Androgen insensitivity syndrome

- Third most common cause of primary amenorrhea
- Patients with CAIS have normal female external genitalia with 46,XY karyotype
- Peripheral androgen resistance due to androgen receptor mutations
- Mutation of AR gene located on X chromosome(Xq11-12)
- X-linked recessive inheritance
- Testosterone: normal or high in male range
  E2: normal or high in male range, LH high, FSH normal or slightly high
- Workup: genetic testing (AR gene)

Journal of Endocrinological Investigation. 2023, 46:2237–2245
Lancet. Vol 380 October 20, 2012

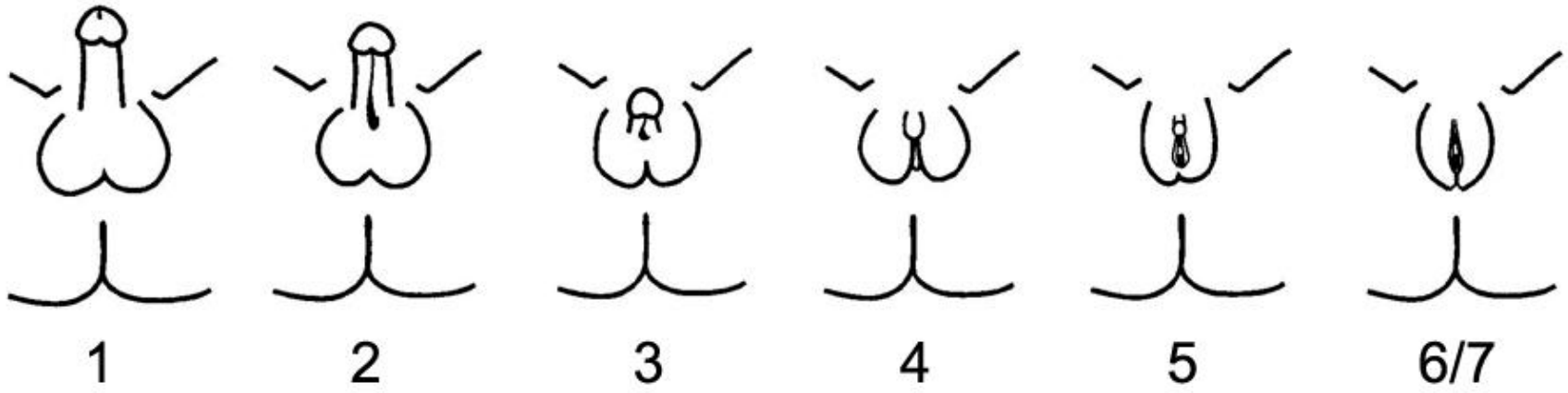






Intractable & Rare Diseases Research. 2023; 12(2):71-77.

Quigley scale



- 1 to 7 in order of increasing severity (more defective masculinization)
- Grade 1 - Typical virilization in utero
- Grade 2 - Male phenotype with mild undervirilization e.g. isolated hypospadias
- Grade 3 – Male phenotype with severe undervirilization e.g. micropenis, perineoscrotal hypospadias, bifid scrotum and/or cryptorchidism
- Grade 4 – severe genital ambiguity, with intermediate phallic size, separated labioscrotal folds, and single perineal orifice
- Grade 5 – Minimally virilized phenotype, with posterior labial fusion and clitoromegaly
- Grade 6/7 – Typical female external genital appearance (grade 6 if pubic hair present inn adulthood, grade 7 if no pubic hair in adulthood)

Endocrine Reviews. Volume 16, Issue 3, 1 June 1995, 271–321

Features	Complete AIS	Partial AIS	Mild AIS
Breast development	Fully developed (female like)	Variable(maybe underdeveloped or asymmetric)	Gynecomastia in puberty
Axillary and pubic hair	Scanty or absent	Scanty	reduced
Gonad	Inguinal, labial, or abdominal testes	Undescended or in labioscrotal fold	Typically intrascrotal (maybe inguinal)
Clinical presentation	Primary amenorrhea Inguinal or labial testes Female ext. genitalia with short blind-ending vagina Scant or absent pubic and/or axillary hair	**Predominantly female :** Clitoromegaly, and labial fushing, Short blind-ending vagina **Ambiguous** : Microphallus with clitoris-like underdeveloped glans, labia majora like bifid scrotum, perineoscrotal hypospadias **Predominantly male :** Clitoromegaly and labial fusion, sinus urogenitalis with a wide opening, Slight signs of androgen effects: slight clitoromegaly or partial labial fusion	Impaired spermatogenesis/ Impaired pubertal virilization
Wolffian duct	Present(hypoplastic)		
Müllerian duct	Absent		
Testosterone	Normal or high in male range		
LH	high	Normal or slightly high	
FSH	Normal or slightly high		
Estradiol	Normal or high in male range		

Adapt from Intractable & Rare Diseases Research. 2023; 12(2):71-77.

hCG stimulation test in diagnosis of 46,XY DSD

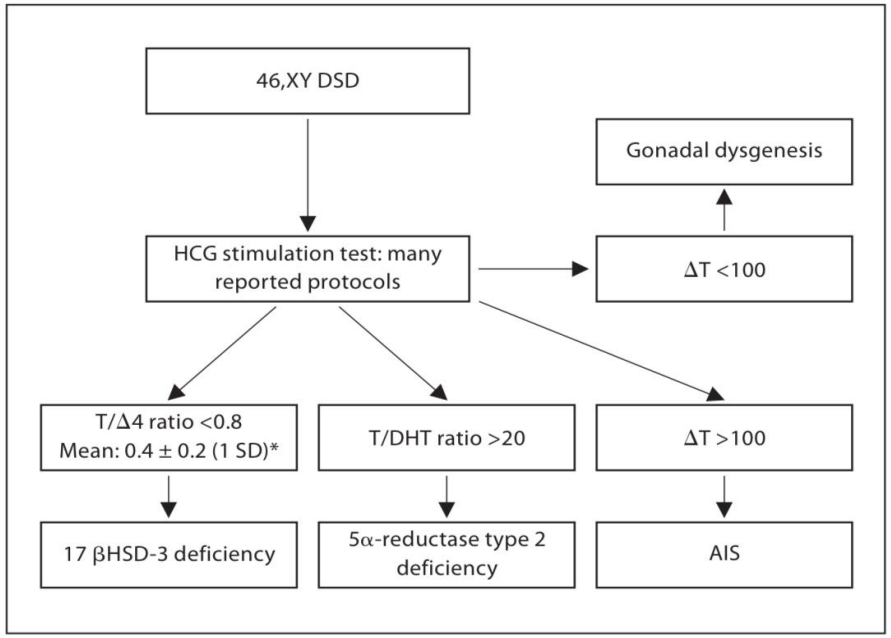


Fig. 2. A simple diagnostic algorithm to elucidate the various etiologies of 46,XY DSD. The diagram shows the importance of hCG stimulation in the diagnosis of 46,XY DSD. Upon hCG stimulation, if the T/Δ4 ratio is <0.8, the diagnosis of 17βHSD-3 can be suspected; if the T/DHT ratio is >20, a diagnosis of 5α-reductase deficiency can be suspected. If the response of testosterone is >100 ng/dl, AIS is possible. However, if the response is <100 ng/dl, causes of gonadal dysgenesis should be sought. Once a diagnosis is suspected, molecular genetic studies can be used for definitive diagnosis [29].

Horm Res Paediatr. 2010;74:229–240

Management for CAIS

- Assignment of an appropriate sex
- Gonadectomy and hormone replacement
- Vaginoplasty / Vaginal dilation (if needed)
- Fertility management
- Psychological concerns and genetic counseling

Management for CAIS

Time of Gonadectomy and Risk of Malignancy

- Pro-gonadectomy perspective: CAIS is associated with an increased risk of testicular germ cell tumors (TGCT).
- The most common tumor types include gonadoblastoma, dysgerminoma, or seminoma, with an estimated risk of 0.8% to 2%.(up to 22% in adult)
- In prepubertal CAIS, the incidence of invasive cancer is very low (<1%)

Int. J. Environ. Res. Public Health. 2019, 16, 1268

Management for CAIS

Time of Gonadectomy and Risk of Malignancy

- In CAIS, the progression from pre-GCNIS to invasive TGCT is rare and typically occurs in late adulthood.
- Two gonadectomy options:
    - Early gonadectomy in infancy, with induced puberty later.
    - Delaying gonadectomy until after puberty allows for natural pubertal development, due to peripheral aromatization of testosterone into estradiol.

Int. J. Environ. Res. Public Health. 2019, 16, 1268

Management for CAIS

- **Adult women with CAIS**, HRT should be continued (after bilateral gonadectomy) until the average age of menopause, essential for maintaining secondary sex characteristics, prevent bone demineralization, cardiovascular and neurocognitive health status

Journal of Endocrinological Investigation . 2023 , 46:2237–2245

Management for CAIS

- The most widely used formulations :
  - Transdermal 17β-estradiol(gel or patch), Micronized oral 17β-estradiol
- Replacement therapy in adult dose
  - E2 transdermal gel 1-3 pumps daily
  - E2 transdermal patch 25-100 μg/twice weekly
  - E2 oral 1-4 mg/day
- The additional therapy with **progesterone is not required** because of the absence of a uterus

Journal of Endocrinological Investigation .2023, 46:2237–2245

Management for CAIS

Vaginal Management

- Vaginal surgery is rarely required.
- First-line treatment: use of vaginal dilators

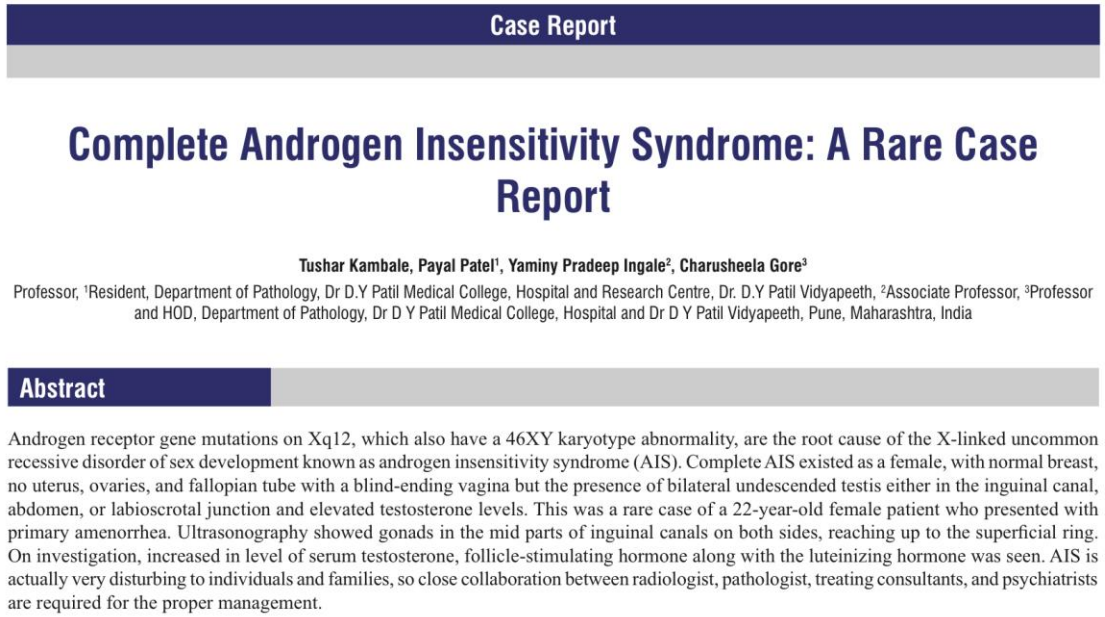
Fertility

- Adoption
- Donor oocytes + surrogate pregnancy using partner's sperm

Psychological concerns and genetic counseling

Lancet. Vol 380 October 20, 2012

CAIS with low testosterone



Case Report

Complete Androgen Insensitivity Syndrome: A Rare Case Report

Tushar Kambale, Payal Patel[1], Yaminy Pradeep Ingale[2], Charusheela Gore[3]

Professor, [1]Resident, Department of Pathology, Dr D.Y Patil Medical College, Hospital and Research Centre, Dr. D.Y Patil Vidyapeeth, [2]Associate Professor, [3]Professor and HOD, Department of Pathology, Dr D Y Patil Medical College, Hospital and Dr D Y Patil Vidyapeeth, Pune, Maharashtra, India

Abstract

Androgen receptor gene mutations on Xq12, which also have a 46XY karyotype abnormality, are the root cause of the X-linked uncommon recessive disorder of sex development known as androgen insensitivity syndrome (AIS). Complete AIS existed as a female, with normal breast, no uterus, ovaries, and fallopian tube with a blind-ending vagina but the presence of bilateral undescended testis either in the inguinal canal, abdomen, or labioscrotal junction and elevated testosterone levels. This was a rare case of a 22-year-old female patient who presented with primary amenorrhea. Ultrasonography showed gonads in the mid parts of inguinal canals on both sides, reaching up to the superficial ring. On investigation, increased in level of serum testosterone, follicle-stimulating hormone along with the luteinizing hormone was seen. AIS is actually very disturbing to individuals and families, so close collaboration between radiologist, pathologist, treating consultants, and psychiatrists are required for the proper management.

22-year-old female with primary amenorrhea

FSH 38.55 mUI/ml, LH 40.04 mUI/ml

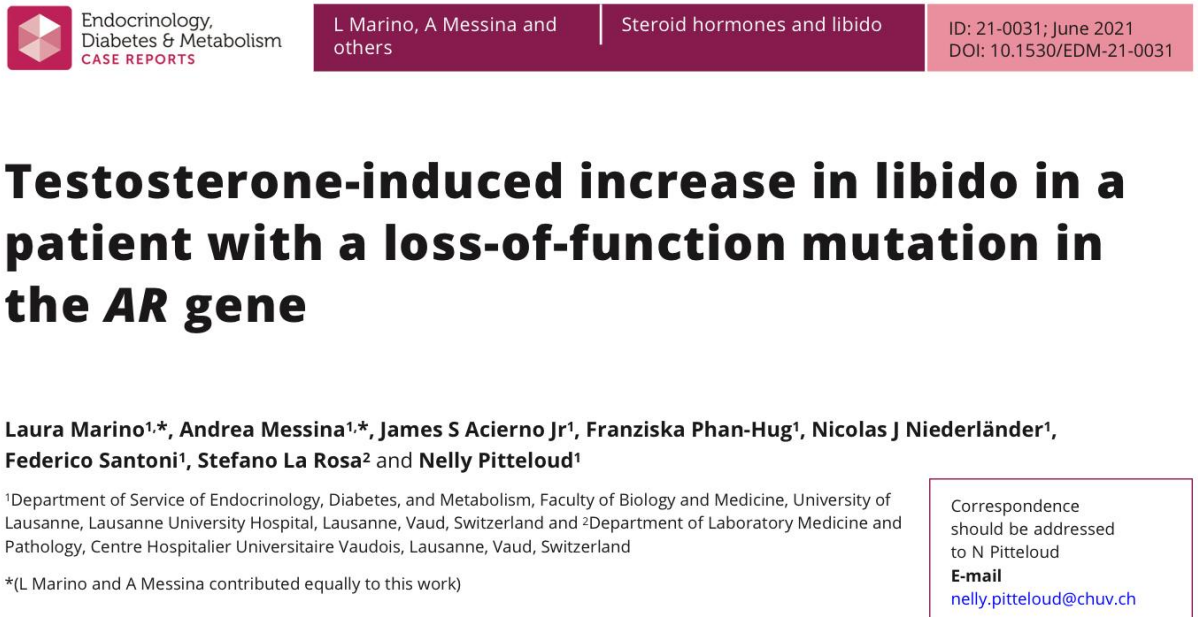
Testosterone 162.22 ng/dl

Karyotype: 46,XY

AR gene analysis: none

Patho: Both testes

National Journal of Clinical Anatomy .Volume 11 October,2022



Endocrinology, Diabetes & Metabolism CASE REPORTS

L Marino, A Messina and others | Steroid hormones and libido | ID: 21-0031; June 2021 DOI: 10.1530/EDM-21-0031

Testosterone-induced increase in libido in a patient with a loss-of-function mutation in the *AR* gene

Laura Marino[1,*], Andrea Messina[1,*], James S Acierno Jr[1], Franziska Phan-Hug[1], Nicolas J Niederländer[1], Federico Santoni[1], Stefano La Rosa[2] and **Nelly Pitteloud[1]**

[1]Department of Service of Endocrinology, Diabetes, and Metabolism, Faculty of Biology and Medicine, University of Lausanne, Lausanne University Hospital, Lausanne, Vaud, Switzerland and [2]Department of Laboratory Medicine and Pathology, Centre Hospitalier Universitaire Vaudois, Lausanne, Vaud, Switzerland

*(L Marino and A Messina contributed equally to this work)

Correspondence should be addressed to N Pitteloud
E-mail
nelly.pitteloud@chuv.ch

26-year-old female with primary amenorrhea

Testosterone 230 ng/dl

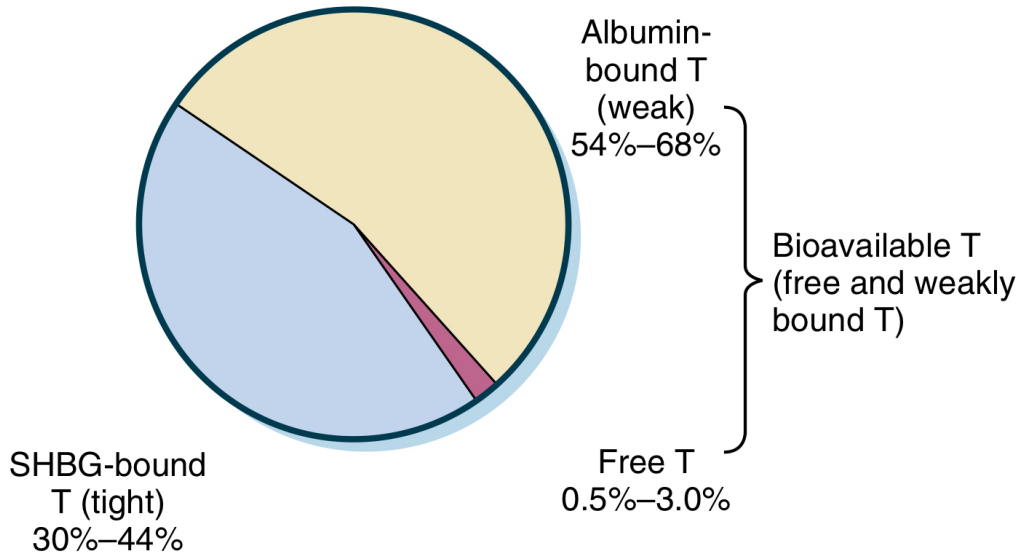
Karyotype: 46,XY

AR gene analysis: p.Glu2_Met190del (c.2T>C)

Patho: Both testes

Endocrinol Diabetes Metab Case Report.June ,2021

Testosterone



• **Fig. 17.10** Fractions of circulating testosterone in blood. The majority of circulating testosterone *(T)* is bound to serum proteins: approximately 54% is weakly bound to albumin, and 44% is tightly bound to sex hormone–binding globulin (SHBG). Only about 2% of circulating T is free of protein binding. The combination of free and weakly bound (albumin-bound) T is referred to as *bioavailable testosterone.*

Table 2. Conditions in Which Measurement of FT Concentration Is Recommended

1. Conditions that are associated with decreased SHBG concentrations
Obesity
Diabetes mellitus
Use of glucocorticoids, some progestins, and androgenic steroids
Nephrotic syndrome
Hypothyroidism
Acromegaly
Polymorphisms in the SHBG gene

WILLIAMS TEXTBOOK OF ENDOCRINOLOGY FIFTEENTH EDITION

J Clin Endocrinol Metab. May 2018, 103(5):1715–1744

Thank you