Sex Chromosome Disorders

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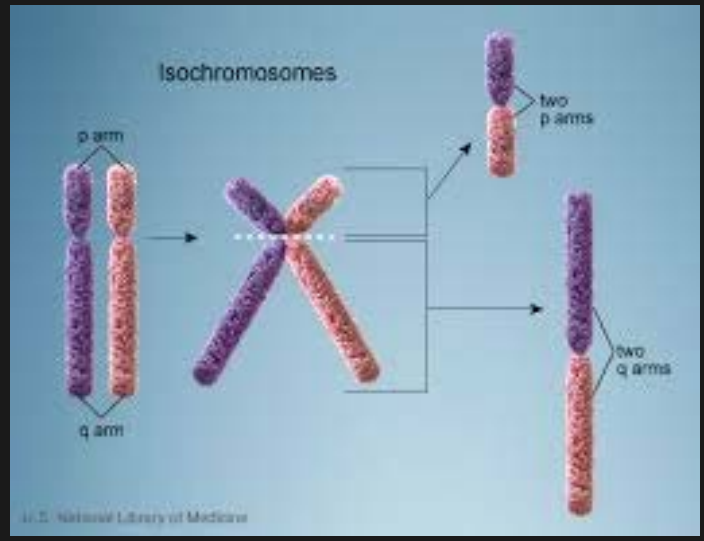
Genetics 2020

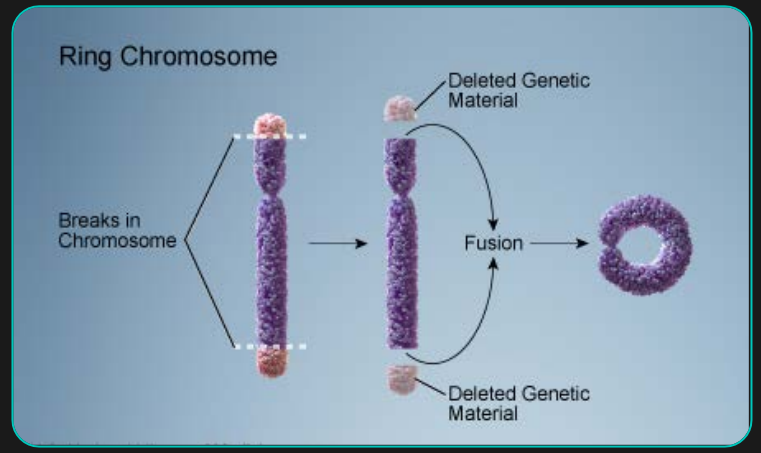
Turner Syndrome: Epidemiology

- Most common sex chromosome disorder
- 1 in 2000-2500 live births
- >99% of chromosome X monosomy do not survive to birth

Turner Syndrome: Genetics

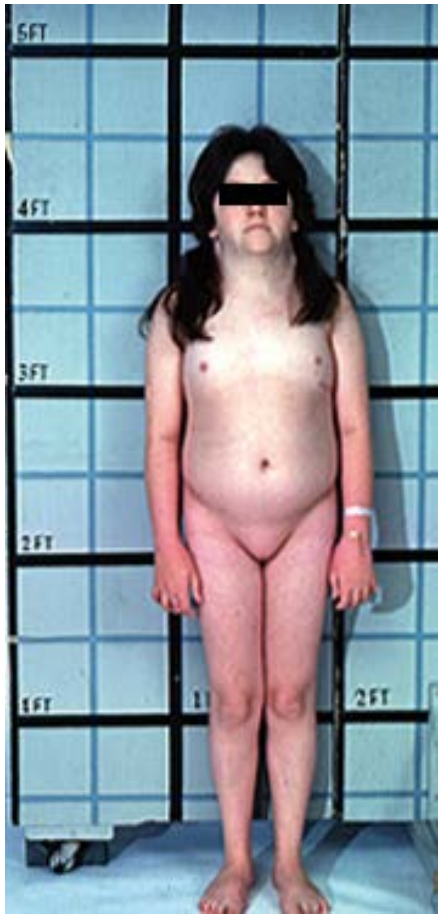
- Pathogenesis
  - 45,X
    - ~50% of Turner live births
    - Secondary toss of sex chromosome in gametogenesis
    - X chromosome from mother two thirds of the time and father in one third
  - 45,X mosaicism
    - ~20% of cases
    - Secondary to nondisjunction during embryo development
  - X chromosome anomalies/fragmentation
    - Isochromosome Xq, Ring chromosome X, Xp or Xq deletion
- The missing chromosomal information can be directly associated with some of the phenotype
  - X chromosome contains SHOX (short stature homeobox-containing gene), and the absence is related to short stature





Turner Syndrome: Features

- MSK and physical features
  - Short stature (most common and consistent finding)
  - Scoliosis (20%)
  - Kyphosis (50%)
  - Wide spaced nipples
  - Webbed neck
- Reproductive
  - Primary hypogonadism
  - Streak ovaries
  - Most have primary amenorrhea and no breast development
- CHD (50%)
  - Aortic valve abnormality (bicuspid aortic valve)
  - Coarctation of the Aorta
  - ASD and VSD (1-4%)
- Renal anomalies (30-40%)
  - Horseshoe kidney
- Sensorineural hearing loss (present in 50% by adulthood)
- Autoimmune disease
  - Thyroid disease (autoimmune thyroiditis) (37%)
  - Celiac (25%)
- Typically normal intelligence but sometimes



Turner Syndrome: Diagnosis

- Diagnostic test is Karyotype
- Who to test?
  - Any girl with one of the following
    - Fetal cystic hygroma or hydrops
    - Idiopathic short stature
    - Unexplained delayed puberty
    - Certain CHD (bicuspid aortic valve, coarct, aortic stenosis)
  - Any girl with two of the following
    - Renal anomaly (horseshoe, absence, hypoplasia)
    - Madelung deformity (increased interosseous space)
    - Multiple typical or melanocytic nevi
    - Dysplastic or hyperconvex nails
    - Hearing impairment <40 years old in someone with short stature

Turner Syndrome: Management

In infancy or time of diagnosis

- 4 extremity BP screening
- ECG and Echo
- Renal US

Surveillance

- Cardiac
  - Periodic echos to monitor for aortic dilation
- Development
  - Annual behavioral and development screening with referrals as needed
  - Audiology eval every 3 years
- Lab work
  - Tissue transglutaminase IgA every 2 years
  - TSH and free T4 annually starting at age 4
  - AST, ALT, Hgb A1c annually starting at age 10
  - Vit D every 2-3 years starting at age 9-11

Turner Syndrome: Management

Growth

- No need to test for GH as girls with Turner are not GH deficient
- Initiate GH therapy once height falls <5%
- Starting GH therapy at a young age (<6) often allows for normal adult height

Hypogonadism and delayed puberty

- Estrogen replacement therapy if no breast development by age 11-12
- Even girls who have spontaneous puberty still usually need estrogen replacement secondaryto eventual ovarian failure

Klinefelter Syndrome: Epidemiology

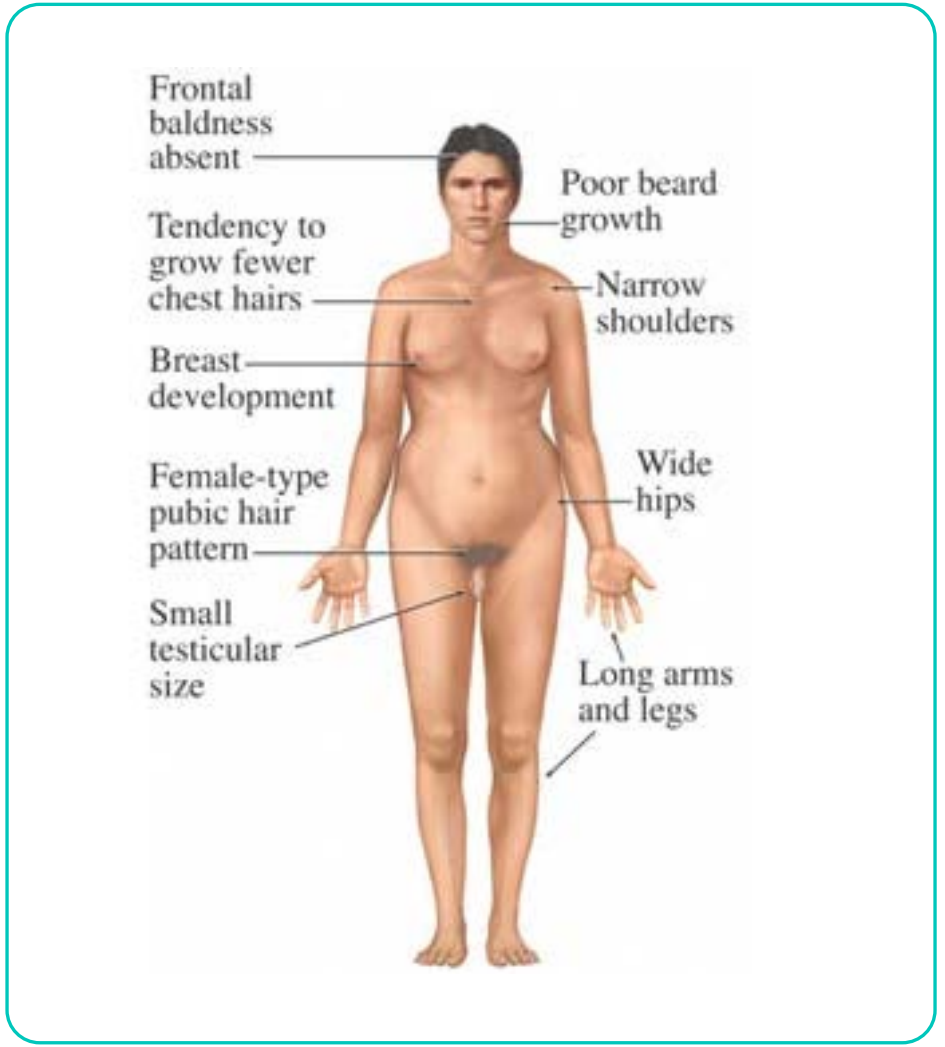
- 1 in 1000 newborns
- 3% of males in infertility clinics
- Diagnosis rarely made before puberty
- Most common cause of primary hypogonadism

Klinefelter Syndrome: Genetics

- Supernumerary X chromosomes in XY male
  - 47, XXY secondary to paternal meiotic nondisjunction (80-90%)
  - Mosaicism secondary to post fertilization mitotic nondisjunction(47,XXY/46XY) (10%)
  - > 2 X chromosomes (i.e. 48,XXXY) (rare)

Klinefelter Syndrome: Features

- Neonatal period and prepubescent
  - Typically no features in this period
  - Possible: micropenis, behavioral problems, learning difficulties
- Puberty
  - Most typical time of diagnosis due to lack of expected pubertal development
  - Failure of testes growth
  - Gynecomastia
  - Taller than expected from mid-parental height with leg growth > arm growth
- Adulthood
  - Infertility
  - Androgen deficiency
  - Small, firm testes
- General
  - Learning disability (>75%), speech delay (40%), ASD (30-50%)
  - Metabolic syndrome (40-50%), T2DM (10-40%)
  - Increased risk of breast cancer (50 fold higher, but lifetime risk <1%)



Klinefelter Syndrome: Diagnosis and Management

Definitive diagnosis is Karyotype

Screening/surveillance

- Breast exam every 1-2 years
- Most other screening based on symptoms

Management

- Only mainstay of treatment is testosterone therapy
  - If micropenis penis present at birth, can use a short course of testosterone in the neonatal period
  - Treatment in puberty with the goal of gradual virilization
- Fertility
  - Progressive testicular fibrosis usually makes unassisted reproduction unlikely
  - 45-50% of men will have success with sperm retrieval

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