Klinefelter Syndrome

Contents

In 1942, Klinefelter et al. (1942) published a report on nine men who had enlarged breasts, sparse facial and body hair, small testes, and an inability to produce sperm. In 1959, these men with Klinefelter syndrome were discovered to have an extra sex chromosome (genotype XXY) instead of the usual male sex complement (genotype XY).

Klinefelter syndrome is the most common sex chromosomal disorder associated with male hypogonadism and infertility. Approximately 1 in 500–1,000 males is born with an extra X chromosome. Over 3,000 affected males are born yearly in the USA.

Synonyms and Related Disorders

47,XXY syndrome; Klinefelter syndrome mosaicism (46,XY/47,XXY, 46,XY/48,XXXY, 47,XXY/48,XXXY); Klinefelter syndrome variants (48,XXYY, 48,XXXY, 49,XXXYY, 49,XXXXY); Klinefelter syndrome with structurally abnormal X chromosome [47,X,i(Xq)Y, 47,X,del(X)Y]

Genetics/Basic Defects

1. Caused by at least an additional X chromosome in a male
2. The XXY form of Klinefelter syndrome:
    1. Due to meiotic nondisjunction of the sex chromosomes during gametogenesis in either parent
    2. Responsible meiotic nondisjunction (Carothers and Filippi 1988; Harvey et al. 1990):
        1. About 40% occur in the father.
        2. About 60% occur in the mother:
            1. Meiosis I errors (75%) when origin is maternal
            2. The presence of maternal age effect in the maternally derived cases
3. The mosaic forms of Klinefelter syndrome:
    1. Due to mitotic nondisjunction after fertilization of the zygote
    2. Can arise from a 46,XY zygote or a 47,XXY zygote
4. The variant forms:
    1. 48,XXXY: nondisjunction occurring either at the first or second meiotic divisions of oogenesis, resulting in an XXX ovum which is then fertilized by a Y-bearing sperm.

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2. 49,XXXXY: Please refer to 49,XXXXY chapter.
3. 48,XXYY and 49,XXXYY: occurrence of nondisjunction in paternal meiosis to have two Y chromosomes:
    1. An X ovum fertilized by an XYY sperm arising from successive nondisjunction in the first and second meiotic divisions
    2. An XX ovum from 47,XXX mother fertilized by a YY sperm

5. Pathophysiology (Chen 2015):
    1. The X chromosome carries genes that play roles in many body systems, including testis function, brain development, and growth (Giedd et al. 2007).
    2. The addition of more than one extra X or Y chromosome to a male karyotype results in variable physical and cognitive abnormalities.
    3. In general, the extent of phenotypic abnormalities, including mental retardation, is directly related to the number of supernumerary X chromosomes.
    4. As the number of X chromosomes increases, somatic and cognitive development are more likely to be affected.

Clinical Features

1. Growth (Chen 2015):
    1. Infants and children: normal heights, weights, and head circumferences
    2. Adolescents and adults:
        1. Eunuchoid body habitus
        2. Usually taller than average
        3. Disproportionately long arms and legs (Ratcliffe et al. 1982)
2. Mild developmental, learning, and behavioral difficulties (70% of patients) (Geschwind et al. 2000):
    1. Delayed speech and language acquisition
    2. Academic and reading difficulties
    3. Attention deficit disorder
    4. Poor self-esteem
    5. Insecurity
    6. Shyness
    7. Poor judgment
    8. Inappropriate assertive activity
    9. Decreased ability to deal with stress
    10. Fatigue
    11. Weakness
    12. Impeded psychosocial adaptation (Bender et al 1995)
3. CNS:
    1. Normal intelligence in most cases
    2. Subnormal intelligence or mental retardation associated with a higher number of X chromosomes
    3. Diminished short-term memory
    4. Prone to epilepsy and essential tremor (Boltshauser et al. 1978)
    5. Psychiatric disorders involving anxiety, depression, neurosis, and psychosis: more common than general population
4. Taurodontism (enlargement of the molar teeth by an extension of the pulp): present in about 40% of patients (vs. 1% in normal XY individuals)
5. Cardiac and circulatory problems:
    1. Mitral valve prolapse (55% of patients)
    2. Varicose veins (20–40% of patients):
        1. Venous ulcers
        2. Deep vein thrombosis
        3. Pulmonary embolism
6. A slightly increased risk of autoimmune disorder:
    1. Rheumatic diseases (Rovensky et al. 2010):
        1. Inflammatory rheumatic diseases
        2. Rheumatoid arthritis
        3. Juvenile idiopathic arthritis
        4. Psoriatic arthritis
        5. Polymyositis/dermatomyositis
        6. Systemic lupus erythematosus
        7. Systemic sclerosis
        8. Mixed connective tissue disease
        9. Antiphospholipid syndrome
        10. Ankylosing spondylitis
    2. Thyroid disease (Campbell and Price 1979)
    3. Sjogren syndrome
    4. Diabetes mellitus
7. Sexual characteristics:
    1. Gynecomastia secondary to elevated estradiol levels and increased estradiol/testosterone ratio:

1. Develop by late puberty in 30–50% of boys with Klinefelter syndrome
2. Risk of developing breast cancer: at least 20 times higher than normal

2. Lack of secondary sexual characteristics secondary to decrease in androgen production:
   1. Sparse facial, body, and sexual hair
   2. High-pitched voice
   3. Female type of fat distribution
3. Male psychosexual orientation in most patients
4. Subnormal libido
5. Erectile dysfunction
6. Oligospermia or azoospermia
7. Testicular dysgenesis in postpubertal patients (Schwartz and Root 1991):
   1. Small, firm testes
   2. Testis size <10 mL
8. Infertility and azoospermia resulting from atrophy of the seminiferous tubules:
   1. Seen practically in all patients with a 47, XXY karyotype.
   2. Klinefelter syndrome mosaics (46,XY/47,XXY) can be fertile.

8. Other characteristics:
   1. Some KS males present with no severe clinical features and lead normal lives, while others exhibit developmental, physical, behavioral, and learning disabilities and disorders (Bird and Hurren 2016).
   2. An increased prevalence of extragonadal germ cell tumors in the mediastinum (Völki et al. 2006) and brain.
   3. More common varicose veins, venous stasis ulcers (Verp et al. 1983; Veraart et al. 1995), and thromboembolic disease.
   4. The syndrome may go undiagnosed in the majority of affected men.
9. Klinefelter syndrome mosaics and variants:
   1. Klinefelter syndrome mosaic (46,XY/47,XXY):
      1. Less severe manifestations
      2. May have normal-sized testes
      3. Less severe endocrine abnormalities
      4. Less common gynecomastia and azoospermia
      5. Occasional fertile men
   2. Klinefelter syndrome variants (Visootsak and Graham 2006):
      1. 48,XXYY variant (Tartaglia et al. 2008):
         1. Tall stature.
         2. Disproportionately long lower extremities.
         3. Clinodactyly.
         4. Pes planus.
         5. Hypertelorism.
         6. Dental problems.
         7. Gynecomastia.
         8. Intention tremor.
         9. Neurodevelopmental disorders, including developmental delays, ADHD, autism spectrum disorders, mood disorders, and tic disorders.
         10. Unusual dermatoglyphic patterns.
         11. Peripheral vascular disease, especially varicose veins and stasis dermatitis.
         12. Poorly developed secondary sexual characteristics.
         13. Hypogonadism.
         14. Testicular histology similar to that of 47,XXY patients.
         15. The sex chromatin pattern indistinguishable from that of the 47,XXY patients except two fluorescent Y bodies is present in a high proportion of somatic nuclei.
      2. 48,XXXY variant (Venkateshwari et al. 2010):
         1. Moderate to severe mental retardation
         2. Behavior: often immature and consistent with IQ level, typically described as passive, cooperative, and not particularly aggressive
         3. Normal to tall stature
         4. Dysmorphic facies
         5. Radioulnar synostosis
         6. Fifth finger clinodactyly
         7. Hypergonadotropic hypogonadism
         8. Small testes
         9. Signs of androgen deficiency
      3. 49,XXXYY variant:
         1. Mental retardation
         2. Somatic anomalies
         3. Small testes

4. 49,XXXXY variant (Zaleski et al. 1966; Peet et al. 1998): severity and frequency of somatic anomalies increase as the number of X chromosomes increases:
    1. Mental retardation
    2. Microcephaly
    3. Short stature
    4. Hypotonia with lax joints
    5. Facial dysmorphic features: ocular hypertelorism, flat nasal bridge, epicanthal folds, bifid uvula, or cleft palate
    6. Short neck
    7. Congenital heart defects
    8. Radioulnar synostosis
    9. Genu valgum
    10. Pes cavus
    11. Fifth finger clinodactyly
    12. Hypergonadotropic hypogonadism with small genitalia
    13. Behavioral disorders: shy, friendly, occasional irritability, temper tantrums, low frustration tolerance, and difficulty in changing routines

10. Natural history of Klinefelter syndrome: estimated prevalence of phenotypic features (Herlihy et al. 2011; Groth et al. 2013; Nahata et al. 2013; Herlihy and McLachlan 2015):
    1. Prepubertal:
        1. Decreased penile size (10–25%)
        2. Cryptorchidism (27–37%)
        3. Delayed speech and motor development (69–75%)
        4. Learning difficulties (>75%)
    2. Postpubertal:
        1. Infertility (99%).
        2. Small testes (>95%).
        3. Decreased testosterone (63–85%) may present as low mood, reduced libido, fatigue, poor muscle development, generalized weakness, or erectile dysfunction.
        4. Decreased facial and body hair (<80%): often perceived as pubertal delay or incomplete virilization.
        5. Gynecomastia (<56%).
        6. Metabolic syndrome (46%).
        7. Diabetes (10–39%).
        8. Osteopenia (40%) – osteoporosis in up to 10%.

Diagnostic Investigations

1. Cytogenetic studies (Kleczkowska et al. 1988):
    1. Commonest indications: hypogonadism and/or infertility (Abramsky and Chapple 1997).
    2. 47,XXY (80–90%).
    3. Mosaicism (10%): Insisting on an adequate number of cells (at least 50) to be examined during karyotyping is important so as not to miss diagnosing mosaicism (Nor and Jalaludin 2016):
        1. 46,XX/47,XXY
        2. 46,XY/47,XXY
        3. 46,XY/48,XXXY
        4. 47,XXY/48,XXXY
    4. Variants (Linden et al. 1995):
        1. 48,XXYY
        2. 48,XXXY
        3. 49,XXXYY
        4. 49,XXXXY
    5. Structural abnormal X in addition to a normal X and Y:
        1. 47,X,i(Xq)Y
        2. 47,X,del(X)Y
2. Endocrinologic studies:
    1. A variable degree of feminization and insufficient androgenization (Vorona et al. 2007):
        1. Elevated plasma FSH, luteinizing hormone, and estradiol levels
        2. Low plasma testosterone levels in patients age 12–14 years
    2. Subnormal increased testosterone in response to human chorionic gonadotropin administration
3. Imaging studies:
    1. Testis ultrasound (US) (Rocher et al. 2016): The testes of KS men are smaller, more nodular, and more vascularized, and they contain more microliths than those of non-KS infertile men. This combination of US results should lead physicians to request a karyotyping.

2. Echocardiography to demonstrate mitral valve prolapse.
3. Radiography:
    1. Lower bone mineral density
    2. Radioulnar synostosis
    3. Taurodontism
4. Histology:
    1. Small, firm testes
    2. Seminiferous tubular hyalinization, sclerosis, and atrophy with focal hyperplasia of mostly degenerated Leydig cells
    3. Deficient or absent germ cells
    4. Rare spermatogenesis (azoospermia)
    5. Progressive degeneration and hyalinization of seminiferous tubules after puberty in mosaic patients
5. Majority of cases of Klinefelter syndrome are detected via one of the following scenarios (Herlihy et al. 2011; Nahata et al. 2013; Herlihy and McLachlan 2015):
    1. Prenatal (21% of diagnoses):
        1. Klinefelter syndrome may be an incidental finding when a karyotype is conducted following chorionic villus sampling or amniocentesis due to increased risk in pregnancy (high risk of Down syndrome, increased maternal age).
        2. More recently, through chromosomal analysis in noninvasive prenatal testing, which women with both low-risk and high-risk pregnancies are choosing because of high accuracy, low risk to pregnancy, and the rapidly decreasing cost of this testing (Simpson and Samango-Sprouse 2013).
    2. Childhood (12% of diagnoses):
        1. Global developmental delay in infancy (delayed walking or speech development)
        2. Behavioral or learning difficulties in childhood [attention deficit hyperactivity disorder (ADHD), autism]
    3. Puberty (16% of diagnoses):
        1. Incomplete (or perceived delayed) puberty in adolescence
        2. Hypogonadism, gynecomastia, or poor virilization noted by the astute physician
    4. Adulthood (51% of diagnoses):
        1. Fertility investigations
        2. Androgen deficiency in different contexts (e.g., sexual dysfunction, depression, osteoporosis)
    5. Incidental at any age: Karyotyping is carried out where Klinefelter syndrome is not the suspected diagnosis (e.g., investigation of an alternate genetic syndrome or hematological malignancy).

Genetic Counseling

1. Recurrence risk:
    1. Patient's sibs: recurrence risk not increased for nonmosaic patients
    2. Patient's offspring:
        1. Recurrence risk not increased since all 47,XXY individuals are infertile
        2. Report of paternity in nonmosaic 47, XXY males (no other tissues were examined for possible mosaicism with a 46, XY cell line)
    3. A risk of having a 47,XXY offspring in a few 46,XY/47,XXY mosaic patients who fathered a child
2. Prenatal diagnosis:
    1. Cytogenetic analysis of fetal cells obtained from amniocentesis and CVS.
    2. Dilemma for parents since prognosis for the fetus with XXY is good but the possibility of phenotypic abnormalities does exist.
    3. Explanation to each couple about the genetic risks resulting from intracytoplasmic sperm injection (ICSI) (increased risk of sex chromosome and autosome abnormalities).
    4. Sperm fluorescence in situ hybridization analysis in a patient with mosaic Klinefelter's syndrome can provide a rough estimate of the risk of transmission of sex chromosomal aberrations to his offspring. This estimate can be of help to the patient and his female partner in deciding on ICSI and prenatal diagnosis (or preimplantation diagnosis) (Kruse et al. 1998).

5. Preimplantation genetic diagnosis by embryo biopsy offers an efficient tool for embryo selection (Friedler et al. 2001).
6. Preimplantation genetic diagnosis (PGD) is generally offered to couples with KS who undergo successful testicular sperm extraction and intracytoplasmic sperm injection. This technique allows for selecting chromosomally abnormal embryos in order to avoid transferring abnormal embryos (Aksglaede and Juul 2013).
7. Low rates of pregnancy termination for prenatally diagnosed Klinefelter syndrome and other sex chromosome polysomies (Meschede et al. 1998).

3. Management (Mandoki and Sumner 1991):
   1. Speech therapy.
   2. Physical therapy.
   3. Occupational therapy.
   4. Educational services.
   5. Stable and supportive family environment (Bender et al. 1995)
   6. Reassurance of patients that most of the clinical features can be explained by the diminished ability of the testes to produce testosterone.
   7. Testosterone replacement (Nielsen et al. 1988; Winter 1990; Smyth and Bremner 1998): Optimal time to initiate therapy is at age 11–12 years of age to allow for the maximum effect and permit boys to experience pubertal changes with their peers:
      1. Corrects hormone imbalance (symptoms of androgen deficiency)
      2. Improves self-image
      3. Positive effect on mood and behavior (Myhre et al. 1970)
      4. Increase in masculinity
      5. Increase in strength
      6. Increase in libido
      7. Increase in facial and pubic hair
      8. Diminish fatigue and irritability
      9. No positive effect on infertility
   8. Management of gynecomastia:
      1. Androgen replacement therapy effective in achieving regression of less severe gynecomastia in some patients
      2. Reduction mammoplasty or liposuction for severe or psychologically disturbing gynecomastia
   9. Management of infertility (Lanfranco et al. 2004):
      1. Nowadays patients with Klinefelter syndrome, including the nonmosaic type, need no longer be considered irrevocably infertile because intracytoplasmic sperm injection offers an opportunity for procreation even when there are no spermatozoa in the ejaculate.
      2. In a substantial number of azoospermic patients, spermatozoa can be extracted from testicular biopsy samples, and pregnancies and live births have been achieved.
      3. The frequency of sex chromosomal hyperploidy and autosomal aneuploidies is higher in spermatozoa from patients with Klinefelter syndrome than in those from normal men. Thus, chromosomal errors might in some cases be transmitted to the offspring of men with this syndrome.
      4. The genetic implications of the fertilization procedures, including pretransfer or prenatal genetic assessment, must be explained to patients and their partners.
      5. Banking testicular tissue from prepubertal KS boys should be performed only in a research framework (Gies et al. 2016).

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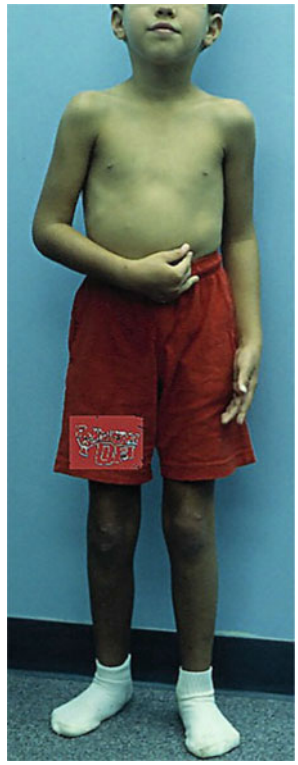

Fig. 1 A child with Klinefelter syndrome (47,XXY) showing normal phenotype

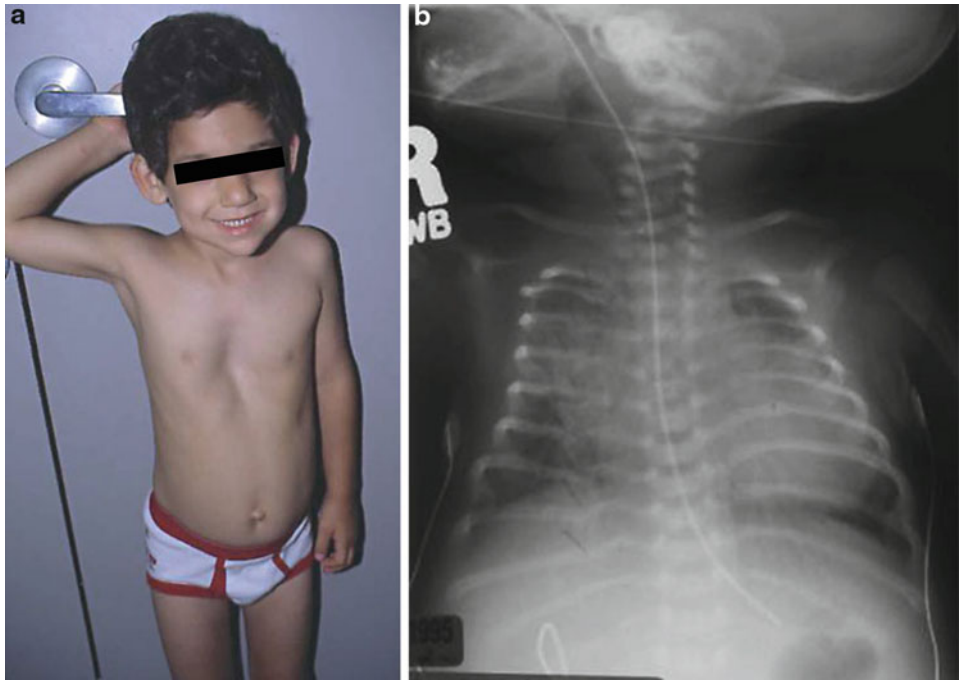

Fig. 2 (**a**, **b**) A child with Klinefelter syndrome (47,XXY) (**a**) showing pectus excavatum and multiple fractures of ribs (**b**) in the neonatal period during hospital stay

Fig. 3 The previous child at 14 years of age

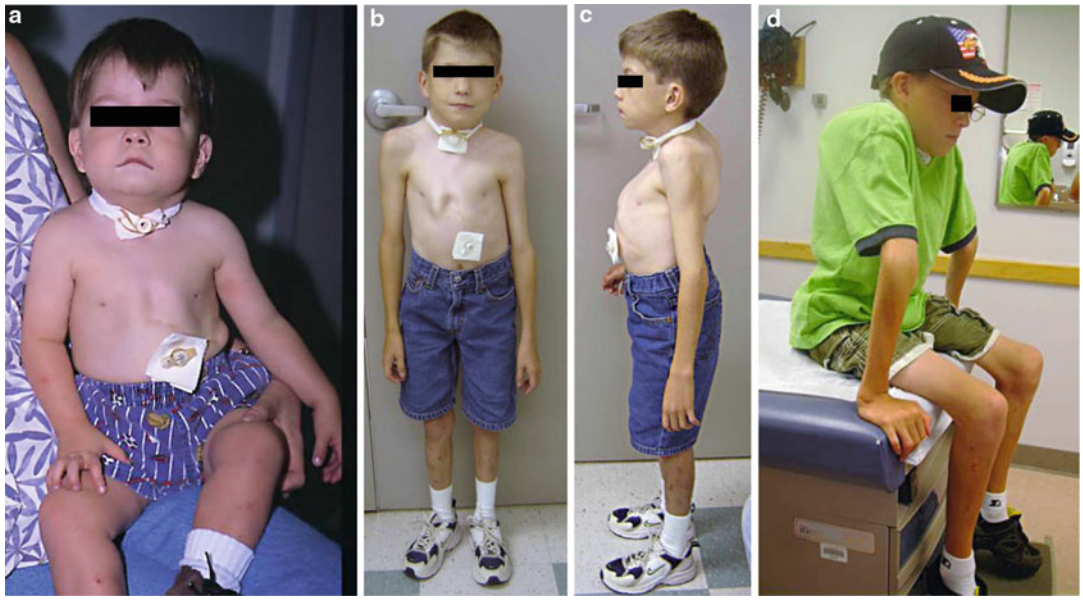

Fig. 4 (**a**–**d**) A child with Klinefelter syndrome (47,XXY) associated with paralyzed diaphragm requiring intubation. The photos were taken at early childhood (**a**), 9 (**b**, **c**), and 12 years of age (**d**) showing pectus excavatum, long extremities with hyperextended elbow, and kyphoscoliosis

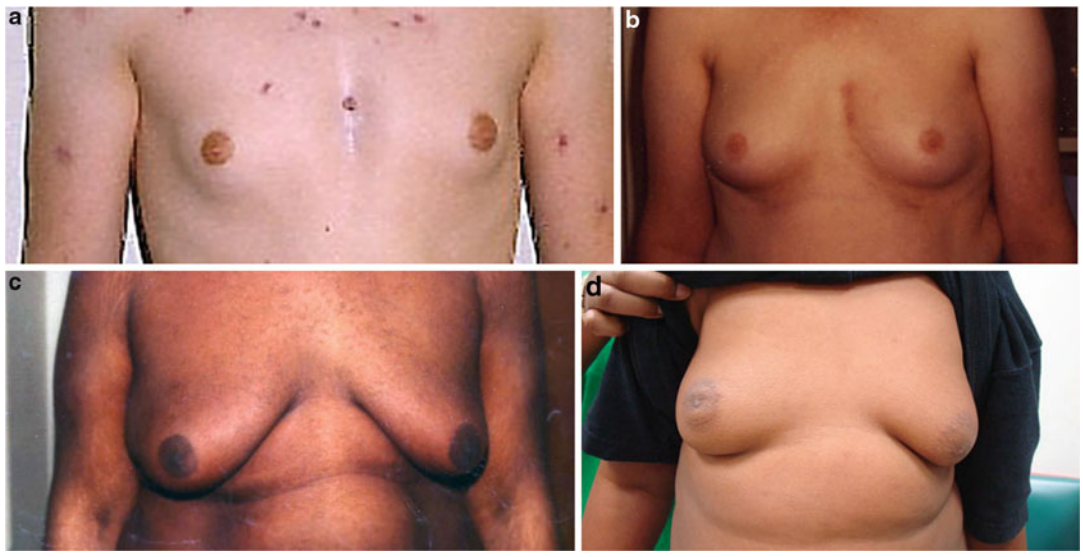

Fig. 5 (**a**–**d**) Two adolescent boys (**a**, **b**) and two adults (**c**, **d**) with Klinefelter syndrome (47,XXY) showing gynecomastia

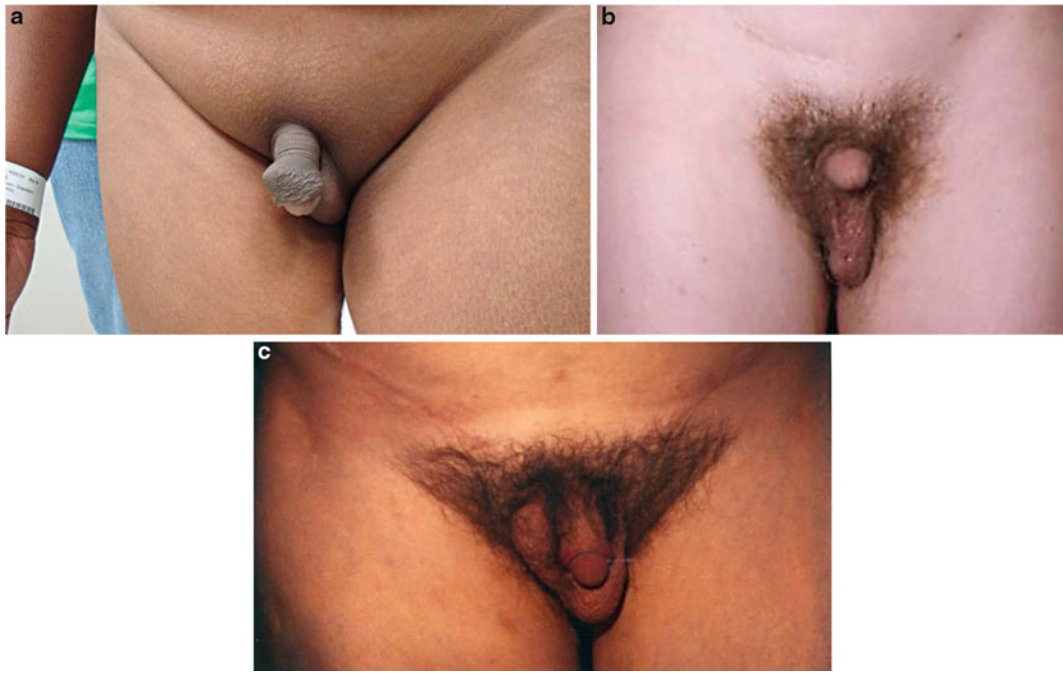

Fig. 6 (**a**–**c**) A 13-year-old boy (**a**), an adolescent boy (**b**), and an adult male (**c**) with Klinefelter syndrome (47,XXY) showing female distribution of pubic hair (last two patients) and small scrotum containing atrophic testicles

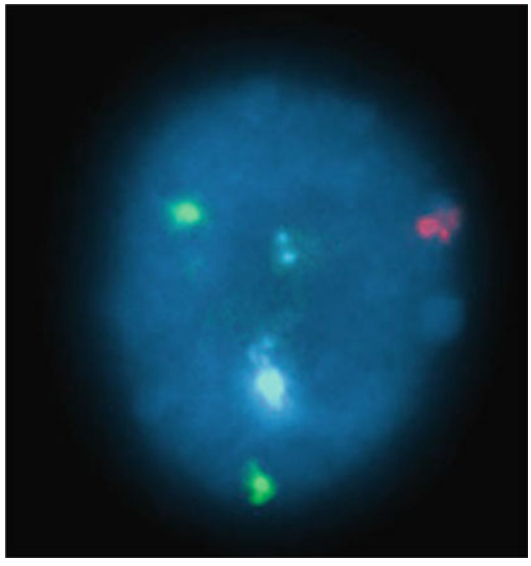

Fig. 7 Interphase FISH showing two copies of CEPX (*green*), one copy of CEPY (*orange*), and two copies of CEP18 (*aqua*), which was confirmed by chromosome karyotype of 47,XXY

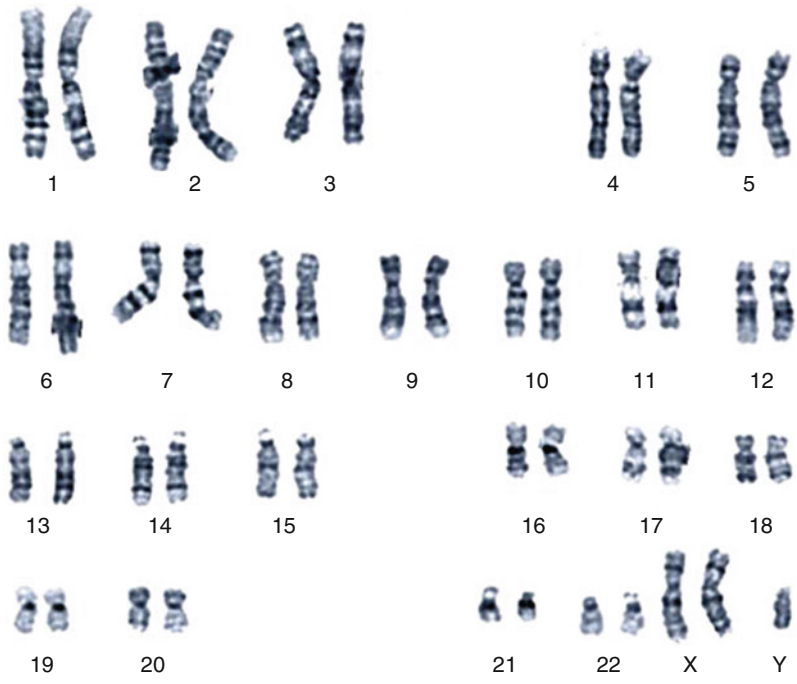

Fig. 8 A G-banded karyotype showing 47, XXY chromosome constitution