

Klinefelter Syndrome

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Klinefelter syndrome is the most common sex chromosome disorder. Affected males carry an additional X chromosome, which results in male hypogonadism, androgen deficiency, and impaired spermatogenesis. Some patients may exhibit all of the classic signs of this disorder, including gynecomastia, small testes, sparse body hair, tallness, and infertility, whereas others, because of the wide variability in clinical expression, lack many of these features. Treatment consists of testosterone replacement therapy to correct the androgen deficiency and to provide patients with appropriate virilization. This therapy also has positive effects on mood and self-esteem and has been shown to protect against osteoporosis, although it will not reverse infertility. Although the diagnosis of Klinefelter syndrome is now made definitively using chromosomal karyotyping, revealing in most instances a 47,XXY genotype, the diagnosis also can be made using a careful history and results of a physical examination, with the hallmark being small, firm testes. As it affects 1 in 500 male patients and presents with a variety of clinical features, primary care physicians should be familiar with this condition.

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Klinefelter syndrome (KS) is a common disorder that affects 1 in 500 male patients and results in testicular failure, androgen deficiency, and impaired spermatogenesis.¹ It was first described in 1942 when Klinefelter et al² described 9 men with gynecomastia, small testes, azoospermia, and elevated gonadotropin levels. They believed that the hypogonadism arose primarily from failure of the Sertoli cells of the testes, the site of spermatogenesis, whereas the appropriate distribution of pubic and axillary hair indicated relatively normal function of the Leydig cells, which produce testosterone. They also suggested that these patients had low or absent levels of a putative second testicular hormone, which regulates the level of pituitary gonadotropins by feedback inhibition, and which they labeled *X hormone* or *inhibin*.²

In 1949, Barr and Bertram³ discovered a dense chromatin mass, later termed

sex chromatin or *Barr body*, in the nerve cell nuclei of female but not male cats. The discovery that Barr bodies are present in the somatic cell nuclei of female but not male human tissue led to the use of smears of stained buccal mucosal cells to determine whether an infant's genetic sex, determined by the presence or absence of a Barr body (presence indicates female sex), matched the phenotypic sex.⁴⁻⁶ In 1956, 2 groups of investigators described 7 patients with KS using results of buccal smears that demonstrated Barr bodies.^{7,8} In 1959, the discovery that a patient with KS had 47 chromosomes, including an extra X chromosome (the karyotype of 47,XXY), established that the Barr body seen in KS represents an additional X chromosome.⁹ Subsequent studies have shown other aberrations of the X chromosome in KS, including 48,XXX and mosaicism, in which 1 cell line has a normal male XY component while another is XXY or some other variant.^{10,11} Barr bodies may not be detected on results of buccal smears in mosaicism, since the oral mucosal cells may

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be the normal XY type, whereas the extra X chromosomes may be detectable only in the testes or peripheral blood cells.¹¹

The presence of an extra X chromosome is considered the fundamental etiologic factor of KS. The constant components of the disorder remain as Klinefelter et al² described, but in contrast to their hypothesis, Leydig cells are hypofunctional, although the testosterone levels may be in the normal range, and patients exhibit diverse degrees of virilization.^{1,11,12} Their hypothesis was correct, however, about the presence of a second testicular hormone. Recent studies have shown that levels of a substance labeled *inhibin B*, the active form of inhibin that originates from Sertoli cells, correlate well with Sertoli cell function and are found at extremely low levels in patients with KS.¹³

PATHOGENESIS

The extra X chromosome in patients with KS is usually acquired through an error of nondisjunction during parental gametogenesis, where a sperm or an egg carries an extra X chromosome in addition to the normal single sex chromosome.¹⁰ It also may result from an error in division during mitosis in the zygote.¹⁰ A study using DNA probes found that paternal nondisjunction accounted for 53.2% of cases, maternal meiotic I errors for 34.4%, maternal meiotic II errors for 9.3%, and postzygotic mitotic errors for only 3.2%.¹⁴ There was a positive correlation between maternal age and maternal meiotic I errors only.¹⁴ That maternal and paternal errors of gametogenesis were almost equally responsible for causing the 47,XXY karyotype contrasts with most cases of autosomal aneuploidy (ie, trisomy 21, as seen in Down syndrome) in which maternal meiosis I accounts for the great majority of errors.^{10,14} This may have relevance in genetic counseling, because in most instances, there is no evidence to suggest that the chromosomal nondisjunction process is more apt to repeat itself in a particular family than would be likely to occur in the general population.

Klinefelter syndrome is a form of primary testicular failure, with el-

evated gonadotropin levels arising from lack of feedback inhibition of the pituitary gland.¹⁵ Although testicular endocrine function may be decreased as early as fetal life, with testosterone levels from umbilical cord blood of infants with XXY being lower than those of control subjects, postnatal pituitary-gonadal function in patients with KS is remarkably normal until puberty.¹⁶⁻¹⁸ Studies of prepubertal boys with an extra X chromosome reveal no difference from prepubertal controls in levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone or in responses to gonadotropin-releasing hormone.^{17,18} By ages 12 to 14 years, however, markedly elevated FSH and LH levels and a plateauing of testosterone levels to the lower half of the normal range or below develop in boys with KS.^{17,18}

Testicular biopsy specimens of infants with this disorder reveal only a reduced number of germ cells¹⁹; after the onset of puberty, however, the pathologic changes characteristic of KS such as hyalinization and fibrosis of the seminiferous tubules appear, leading to small, shrunken testes and azoospermia.^{2,18} This loss of functional seminiferous tubules and Sertoli cells results in a marked decrease in inhibin B levels, presumably the hormone regulator of FSH levels.¹³ In normal male subjects, the pulsatile secretion of LH stimulates the synthesis and secretion of testosterone, which in turn inhibits pituitary LH and FSH secretion.²⁰⁻²² The presence of increased serum LH levels despite low-normal testosterone levels indicates that patients with KS have an altered hypothalamic-pituitary-gonadal axis.^{11,15,23}

The pathogenesis of the gynecomastia in KS remains obscure. The elevated serum estradiol levels observed in patients with KSs, which seem to derive from increased peripheral conversion of testosterone to estradiol and a decreased clearance rate, likely contribute.²³ The histologic changes seen in the gynecomastia of patients with KS, however, are unique in that they show hyperplasia of the interductal tissue, unlike the ductal hyperplasia seen in other high-estrogen states such as cirrhosis of the liver.²⁴

INCIDENCE

Findings of large prospective chromosomal studies of newborns, like earlier results of screening with buccal smears, have demonstrated that KS occurs in about 1 in 500 male births.²⁵⁻²⁹ In more than two thirds of the cases, the karyotype from blood is the classic 47,XXY.²⁵ The prevalence may be greater, however, in certain groups such as patients seen for endocrine, psychiatric, or infertility problems.³⁰⁻³²

CLINICAL MANIFESTATIONS

When Leydig cell failure occurs before puberty, testosterone levels are low, the normal changes of puberty do not develop, and the obvious features of eunuchoidism are present. Features of androgen deficiency include eunuchoidal proportions with abnormally long legs (hips to soles, 2 inches greater than hips to head) and arm span greater than height; sparse or absent facial, axillary, pubic, or body hair; decreased muscle mass, with a feminine distribution of adipose tissue, including gynecomastia; and small testes and penis.²⁰ In many patients, even with classic KS, testosterone levels may be in the normal or low-normal range (**Figure 1**).^{1,11} Total testosterone levels may be falsely high as serum hormone-binding globulin levels in patients with KS are elevated, and free testosterone levels, which may be a more accurate assessment of the androgen status in KS, are low.^{11,23} Serum levels of gonadotropins (particularly FSH) are uniformly elevated in KS.^{1,11} There is a wide variability in clinical expression, related to the timing and amount of androgen deficiency. The distribution of clinical and laboratory values in classic KS^{1,11} are shown in the following tabulation:

Pathologic Feature	% of Patients
Infertility	99-100
Small testes	99-100
Gynecomastia	50-75
Decreased pubic hair	30-60
Decreased facial hair	60-80
Decreased testosterone levels	65-85
Elevated gonadotropin levels	90-100
Decreased penis size	10-25

The constant features of the disorder are small testes and absent spermatogenesis, whereas the fre-

quency of decreased facial and pubic hair, gynecomastia, and low testosterone levels varies. Testis size is uniformly reduced, usually less than 2 cm in length, 1 cm in width, and 4 mL in volume in adults, compared with the normal values of 4 cm, 2.5 cm, and at least 15 mL, respectively.^{11,20,33} In addition, the testes are typically firmer than normal due to the fibrosis of the seminiferous tubules.^{1,11,20}

Mosaic individuals have an even wider diversity of findings, especially in the histologic characteristics of testicular biopsies.^{1,11} Samples from male subjects with XY/XXY genotype reveal that 14% to 61% of their seminiferous tubules contain maturing spermatids, which explains the rare cases of fertility in these patients.^{11,34,35}

The eunuchoidal skeleton often present in KS consists of an increased armspan, which exceeds body length by 2 cm or more, and an above-normal height, usually greater than 184 cm and mostly attributable to abnormally long legs.^{36,37} This increased length of the lower body—from pelvis to soles—is present before puberty and, therefore, does not arise primarily because of delayed epiphyseal closure due to androgen deficiency, but because of a fundamental difference in the growth rate caused by the presence of the additional X chromosome.³⁶⁻³⁸ Testosterone deficiency, however, contributes to the abnormal body proportions, as similar eunuchoidal skeletal features occur in other disorders of androgen insufficiency present before puberty (**Figure 2**).^{36,39}

ASSOCIATED DISORDERS

Cancer

Breast carcinoma is rare in men; its incidence in most populations is less than 1 case per 100 000 man years.³³ However, it is at least 20 times more common in patients with KS, who account for about 4% of all cases.⁴⁰ Although some authors have not found a relationship between KS and male breast cancer,⁴¹ the sample studied may have been too small, as the expected incidence of breast cancer in KS is about 1 case in 5000 men. Nearly all patients with KS and

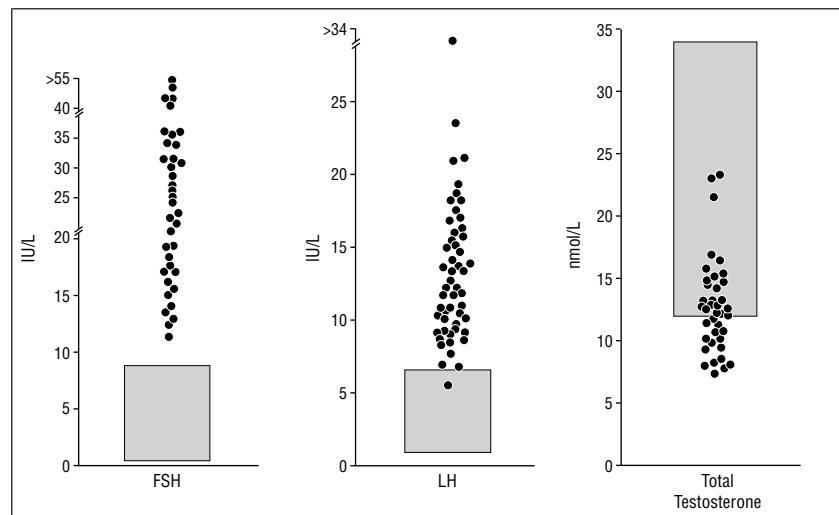


Figure 1. Plasma testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) values in healthy control subjects and patients with Klinefelter syndrome (KS). Shaded bars represent the ranges for controls; dots, values seen in patients with KS. Whereas FSH and LH levels seen in KS are in most cases well above normal, there is a large degree of overlap in total plasma testosterone levels between controls and patients with KS. (C. Alvin Paulsen, MD, unpublished data, January 1975.)

breast cancer have gynecomastia, which may be a predisposing factor.^{24,40} Given this low frequency, there is no evidence to support the use of screening mammography or prophylactic resection of palpably enlarged breasts in KS.^{24,41}

Extragenital germ cell tumors also occur with increased frequency in KS.⁴¹ The typical patient is 15 to 30 years of age and has metastatic disease, usually with mediastinal involvement, at the time of presentation.^{41,42} These neoplasms probably arise from incomplete migration of the primordial germ cells from the endoderm of the yolk sac to the urogenital ridge.⁴¹ The persistently elevated gonadotropin levels in KS may contribute to the malignant transformation of these cells.⁴¹ Even with extensive metastases, however, these tumors are potentially curable with chemotherapy.⁴²

Autoimmune Disorders

The increased incidence of autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, and Sjogren syndrome in patients with KS compared with other male subjects may be due to their lower testosterone and higher estrogen levels, since androgens may protect against, and estrogens promote, autoimmunity.^{43,44} Another hypothesis incriminates the lymphocyte ab-

normalities in KS; the reduced numbers of total lymphocytes and the OKT8+ (suppressor T cells) subtypes results in an increased OKT4:OKT8 ratio, a feature sometimes found in women and eugonadal men with autoimmune disorders.⁴⁴ Supporting this suggestion is the influence of testosterone administration in 5 patients with KS who had clinically active autoimmune disorders, elevated autoimmune antibody titers, increased erythrocyte sedimentation rates, and high OKT4:OKT8 ratios.⁴⁴ Testosterone replacement therapy improved all clinical and immunologic abnormalities and reduced the OKT4:OKT8 ratios.⁴⁴

Intellectual and Psychiatric Disorders

The prevalence of KS among male subjects in mental and penal institutions is about 1%, 5 times higher than in the general population, which has led to the belief that patients with KS are inherently mentally subnormal and prone to criminal behavior.^{31,45-48} Large-scale screening studies have refuted these impressions, but they have demonstrated a higher frequency of learning disabilities and poor impulse control, findings that may explain the increased rate of incarceration.⁴⁷⁻⁵⁰ Although many patients with KS have above-average or superior intelligence, poor school

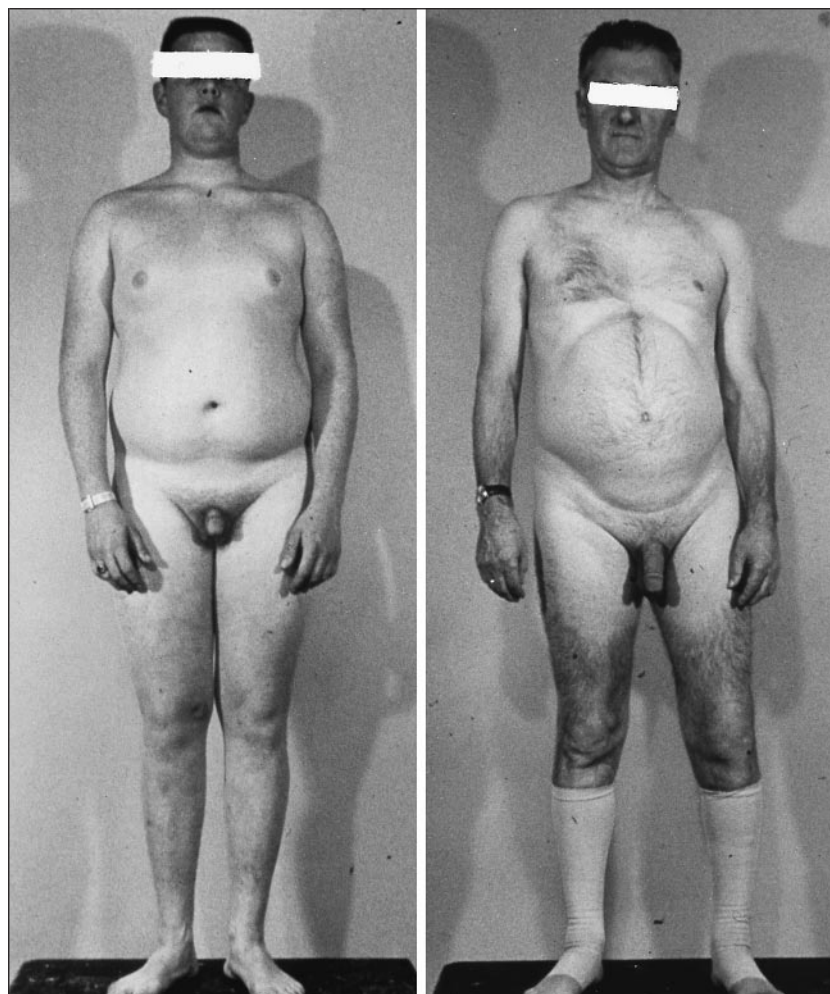


Figure 2. Male subjects with the classic 47,XXY karyotype of Klinefelter syndrome (KS) and mosaicism (XY/XXY). Left, Eunuchoidal proportions, feminine distribution of body fat, gynecomastia, lack of facial, body, and pubic hair, and small penis and testicular size of KS. Right, More androgenized features with a more masculine physique, greater amount of body hair, and a larger penis and testes size in mosaicism. (Reprinted with permission from C. Alvin Paulsen.)

performance is common, with specific reductions in verbal IQ scores, delayed speech and language acquisition, diminished short-term memory, and decreased data retrieval skills.^{24,47,49,50} They may also have a higher incidence of dyslexia and attention-deficit disorder.^{47,49,50} These intellectual difficulties seem to derive from the extra X chromosome, and, indeed, patients with KS variants possessing more X chromosomes (eg, 48,XXXY; 49,XXXXY) have greater incidence of mental retardation.^{10,48}

Psychiatric disorders ranging from anxiety and neuroses to psychosis and depression are common in KS.^{45,47,51} Compared with other boys their age, adolescents with KS consider themselves more sensitive, introspective, apprehensive,

and insecure.^{45,47,49} They also have more problems with peer groups and less sexual interest in girls.⁴⁷ The combination of feminine physical features, poor motor coordination, and difficulties in speech and memory probably impairs the attainment of adequate self-esteem, increases anxiety, and promotes insecurity. The intertwining of these factors makes it difficult to determine what influence, if any, the extra X chromosome or a low androgen state has on human behavior. Testosterone replacement therapy advances the development of secondary sexual characteristics and alters gender identification and subsequent behavior; in addition, it may have independent effects on promoting self-esteem.^{52,53}

Osteoporosis

Androgen deficiency is an important risk factor for osteoporosis in men, and testosterone replacement therapy improves bone mineralization and osteoid formation, in part through the conversion of testosterone to estradiol, which prevents bone breakdown.^{20,54,55} Free testosterone levels are highly correlated with bone mineral density in patients with KS.⁵⁶ Compared with controls, 25% or more of patients with KS have decreases in bone mineral density of 12% to 15%; patients with untreated KS have deficient testosterone levels during puberty and consequently do not achieve a normal peak bone mass.^{18,56} Testosterone replacement treatment before the age of 20 years can improve bone mass to normal values, whereas testosterone replacement therapy begun later produces no significant increase but may help prevent further bone loss and possibly fractures in older men.⁵⁶

Endocrine Disorders

Diabetes mellitus, although more common in patients with KS than in the general population, is generally mild and similar to the adult-onset form.^{38,57} Thyroid reserve levels appear diminished, but whether hypothyroidism is more frequent remains unclear.^{38,58,59} Adrenal function is normal.^{39,53}

Venous Disease

Klinefelter syndrome predisposes patients to various venous diseases. In 1 study, 21 (20%) of 104 patients had varicose veins, which were often severe and appeared at an early age.²⁴ There is a 10- to 20-fold increased prevalence of venous ulcers and an increased risk for deep venous thrombosis and pulmonary embolism, perhaps related to a basement membrane defect in venous valves or an underlying hypercoagulable state.^{10,60,61}

Taurodontism

Taurodontism, an uncommon condition of the teeth affecting 0.5% to 3.0% of the general population, consists of enlargement of the pulp with a thin-

ning of the surface of the tooth.⁶² Although functional, the teeth are prone to early decay.⁶² This disorder is present in more than 40% of patients with KS and becomes more pronounced as the number of extra X chromosomes increase.^{10,62} Dental radiographs, rather than oral inspection, usually establish the diagnosis.⁶²

TREATMENT

Testosterone replacement treatment has no effect on infertility caused by KS, but it corrects the androgen deficiency.⁶³ This therapy results in an increase in facial and pubic hair, a more masculine distribution of body fat, more goal-directed thinking, improved self-esteem, less fatigue and irritability, and increased libido, strength, and bone mineral density.^{24,52,53,56} The optimal time to initiate testosterone replacement therapy is at the beginning of puberty, about age 11 or 12 years.^{18,52} This timing permits boys with KS to experience pubertal changes similar to their peers and allows testosterone to have its most marked effects on bone mineral density.^{18,52,56} When the diagnosis of KS is made in adulthood, testosterone replacement therapy is still beneficial in producing positive changes in mood and behavior, muscle mass, and bone integrity.^{52,53}

The increased testosterone serum levels resulting from this therapy eventually produce a decrease in serum LH and FSH levels.^{11,23} The effect on gonadotropin levels, however, is not so rapid or pronounced as it is in controls.^{22,23} Once begun, testosterone administration should continue throughout life in patients with KS. In addition to its virilizing effects, it also stimulates erythropoiesis and increases the number of suppressor T lymphocytes.^{44,63} It has no effect on testicular size or spermatogenesis, and it usually does not reduce gynecomastia, which can be very well treated with plastic surgery.^{24,53,63}

The most widely used form of androgen replacement therapy is the intramuscular injection of testosterone enanthate and testosterone cypionate, which have similar pharmacokinetics and safety profiles.⁶⁴⁻⁶⁶ Typical doses necessary to maintain

normal serum testosterone levels for an adult with KS are 200 mg of either ester every 2 weeks.^{63,65} When started in puberty, doses are usually 50 to 100 mg initially, with an increase of 50 to 100 mg every 2 to 4 weeks until adult doses are reached.^{18,63} Because of the small testes, the scrotal sac is diminished, and its surface area is insufficient for transdermal preparations of testosterone requiring administration at that site.^{63,64} Although convenient, newer formulations that may be applied on nonscrotal skin are more expensive than intramuscular testosterone preparations, and their use in patients younger than 18 years has not received adequate evaluation.^{63,64}

Weight gain may occur during testosterone replacement therapy, due to the accumulation of lean body mass and fluid.⁶⁴ Mild acne may also occur.⁶⁴ Sleep apnea may occasionally develop in older men and cause erythrocytosis. Androgens also lower high-density lipoprotein levels, so lipoprotein and hematocrit levels should be followed up.⁶⁴ In general, the testosterone esters are well tolerated at replacement doses, and the benefits of increased bone density, a more masculine physique, and overall psychological well-being outweigh these side effects in patients with KS.

SCREENING

The diagnosis of KS may be made in utero when chromosomal karyotyping is performed on a sample of amniotic fluid obtained routinely from pregnant women of advanced maternal age. Parents told of the diagnosis of KS should be carefully counseled on the wide variety of clinical manifestations that may be present in their child. This information can help parents consider testosterone replacement therapy early in puberty and increase their awareness of learning disabilities and gender identification issues that may present during childhood or adolescence.

All school-age boys should have their testes palpated as part of a complete physical examination, and those with learning disabilities or trouble with their peers deserve special attention. Testicular size of less than 4 mL, gynecomastia, taur-

odontism, a postpubertal height greater than 184 cm, abnormally long legs, and an armspan exceeding height are important clues to the diagnosis of KS.^{1,10,11} As hormone values may still be normal, if any of these signs is present, peripheral blood karyotyping can be used to detect extra X chromosomes, but results may be negative in mosaic individuals.¹¹ Although expensive and invasive, testicular biopsy may be appropriate for a patient who wishes to know if any germ cells are present.¹¹ This procedure is also reasonable for chromosomal karyotyping in those with suspicious clinical findings, negative results of peripheral blood karyotyping, and possible mosaicism.¹¹

The diagnosis of KS should be considered in men with complaints related to hypogonadism, ie, fatigue, weakness, gynecomastia, infertility, erectile dysfunction, and osteoporosis.^{20,63,67,68} A hormonal evaluation should be performed to distinguish KS, a disorder of primary testicular failure, from one of secondary hypogonadism or a pituitary process.²⁰ The presence of small testes and low serum testosterone levels with elevated FSH and LH levels is usually sufficient to make the diagnosis.^{1,11} Testosterone replacement treatment should be started early to minimize the physical and psychological effects of androgen deficiency. Knowledge of the diagnosis of KS is important, not only in understanding and treating the manifestations of this disorder but also in making the patient and clinician more alert to the presence or development of associated conditions.⁶⁹

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Physicians and patients interested in obtaining further information about KS, including support group resources, can contact Klinefelter Syndrome and Associates, PO Box 119, Roseville, CA 95678-0119 (e-mail: ks47xy@ix.netcom.com).

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